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EFFECTS OF AN AIR PURIFYING APPARATUS ON RAGWEED POLLEN, MOLD AND BACTERIAL COUNTS

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IN RECENT YEARS, the use of an air conditioning apparatus, both as an air cooler and as a filter of particulate matter in the air, has become widespread. In addition, there have become available many so-called air purifying devices. These devices vary in structure, but claim to have the following functions in common: filtration of air and electrification of air with negative ions. This study was set up for the purpose of determining the effects of each of these devices on the pollen concentrations and bacterial counts of hospital rooms where they were in actual use over a period of time.

PROCEDURE

The two-week period, starting on August 28, 1960 and extending through September 10, 1960, was chosen as the test period. Previous experience over many years[1] had confirmed the fact that the outdoor ragweed pollen counts were at their peak during this period. The study was conducted at the Northern Division, Albert Einstein Medical Center in Philadelphia. Four adjacent rooms, identical in all respects and all facing the same direction (South) were made available on the seventh floor of the new

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medical-surgical building. These rooms were all equipped with Carrier, model 51 W, room air conditioners of three-quarters ton capacity. These units were permanently installed through the wall, below window level, and did not obstruct the windows. According to specifications, the capacity

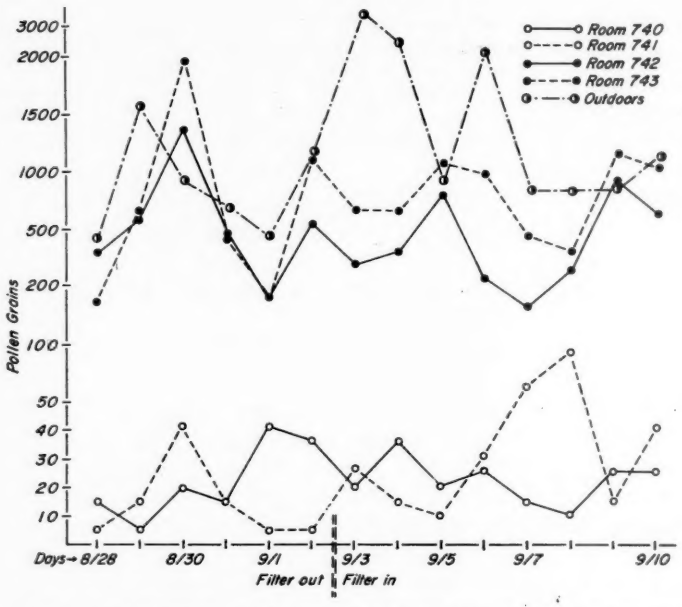

Fig. 1. Pollen counts over the two-week period (August 28, 1960 through September 10, 1960).

of these units was approximately 300 cu ft of air per minute. With the vent open, about 10 per cent of the circulated air, 30 cu ft per minute, was fresh air introduced from the outside, the remainder being recirculated from the atmosphere in the room. During the course of the study the air conditioners and vents were arranged as follows:

Room 740—Air Conditioner in operation with vent open and windows closed.

Room 741—Air Conditioner and air purifier in operation with vent open and windows closed.

Room 742—No air conditioner, windows open.

Room 743—No air conditioner, windows open, plus air purifier.

These rooms were unoccupied and the doors were kept closed at all times. During the first six days, there was no filter in place in the air conditioners. During the remaining eight days, the standard filter was in place.

As was noted above, two of the rooms, one air conditioned, the other not air conditioned, were each equipped with an air purifier. This device had the following specifications:[2]

The F-20 consists of a metal housing (approximately 7″ x 7″ x 10″) containing three ultraviolet lamps and ballast, an impregnated glass filter, and a centrifugal fan and fan motor. Air enters through vents on the top of the unit. The air then passes through the irradiation chamber where it is subjected to ultraviolet irradiation. The air then passes through the impregnated glass filter and out through a series of vents in the front of the machine. The three processes of importance are irradiation, electrification and filtration.

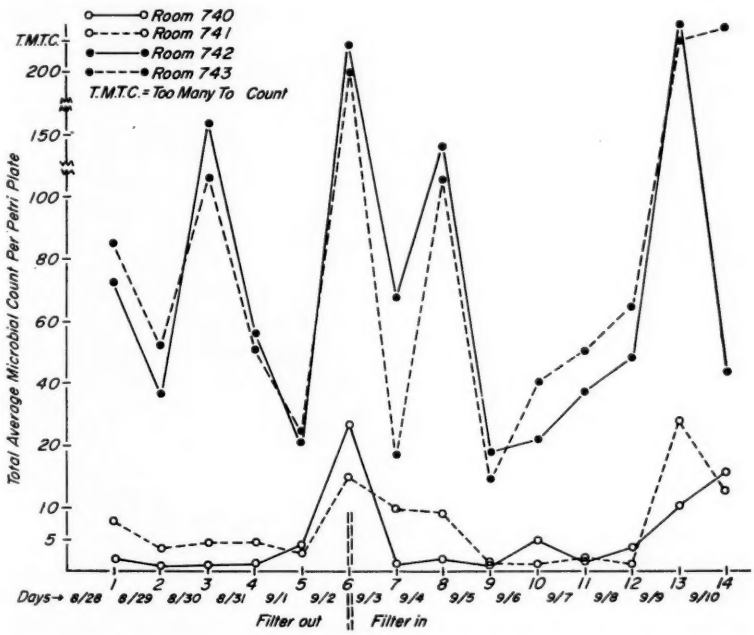

Fig. 2. Bacterial and mold counts over the two-week period (August 28, 1960 through September 10, 1960).

The manufacturer reports the apparatus to have the following performance:

1. Due to filtration and the electrostatic effects, the unit is nearly 100 per cent efficient in the filtering of pollen (ragweed pollen).
2. The net negative electrification of the air is greater than 12,500,000 unit electronic charges per second.
3. The ozone production is 0.086 parts per million at the outlet of the machine.

TABLE I. RAGWEED POLLEN COUNTS
(Filter Absent from Air Conditioner)

Date	Outdoors	Room 740 Air Conditioned	Room 741 Air Conditioned and Puritron	Room 742 Open Windows	Room 743 Open Windows and Puritron
8/28	449	15	5	370	175
8/29	1550	5	15	602	653
8/30	979	20	41	1382	1974
8/31	683	15	15	479	418
9/1	469	41	5	178	178
9/2	1102	37	5	556	1115
Totals	5232	133	86	3567	4513

The volume output of the blower in these units was 30 cu ft of air per minute.

Pollen counts were conducted out of doors, at the seventh floor level, and in each of the experimental rooms. These counts were done using the Marx Volumetric Impinger.[3] The results obtained by this method represent volumetric counts taken over a twenty-four-hour period. The machines were cycled to measure 10 liters of air per minute, approximating the human minute tidal respiratory volume. Over each twenty-four-hour period, the total of 18.4 cu yds of air passed through the impinger, and its pollen content was calculated.

For the bacteriologic phase of this study, nutrient blood agar plates (100 mm diameter) were exposed for twenty-four-hour periods in each of the rooms previously described. Each plate was incubated for twenty-four hours at 37° C, and then at room temperature, followed by a determination of the number of molds, yeasts, bacterial colonies, and total count by standard microbiological methods. Any colonies of special interest, such as unusual organisms or staphylococci, were specially enumerated.

RESULTS

Table I, Table II and Figure 1 show the pollen counts over the two-week period. There is a significant difference in the total counts between the outside, the air conditioned rooms, and non-air conditioned rooms with

TABLE II. RAGWEED POLLEN COUNTS
(Filter Present in Air Conditioner)

Date	Outdoors	Room 740 Air Conditioned	Room 741 Air Conditioned and Puritron	Room 742 Open Windows	Room 743 Open Windows and Puritron
9/3	3820	20	26	326	699
9/4	2606	36	15	398	678
9/5	974	20	10	765	1096
9/6	2071	26	31	240	994
9/7	847	15	66	168	454
9/8	852	10	92	286	377
9/9	867	26	15	959	1158
9/10	1321	26	41	663	1046
Totals	13358	179	296	3805	6502

open windows. There seemed to be little difference noted in the air conditioned rooms with and without filters in place. The extremely low counts in the air conditioned rooms (740 and 741) could possibly be due to the efficiency of the air conditioner in filtering out pollen. The coils and other parts of the air conditioner might act as a baffle and obstruct the course of the pollen. On the other hand, the counts in these rooms might be low because of the fact that relatively small volumes of fresh air were entering the room compared to the free flow of air in the rooms where the

TABLE III. BACTERIAL AND MOLD COUNTS
(Filter Absent from Air Conditioner)

	Contaminant	Room 740 Air Conditioned	Room 741 Air Conditioned and Puritron	Room 742 Open Windows	Room 743 Open Windows and Puritron
8/28	Molds	1	8	32	38
	Staphylococcus	0	0	4	4
	Other colonies	1	0	36	44
	Total	(2)	(8)	(72)	(86)
8/29	Molds	0	3	11	9
	Staphylococcus	0	0	4	0
	Other colonies	0	0	22	6
	Total	(0)	(3)	(37)	(15)
8/30	Molds	1	4	120	80
	Staphylococcus	0	0	3	4
	Other colonies	0	0	40	32
	Total	(1)	(4)	(163)	(116)
8/31	Molds	0	1	16	18
	Staphylococcus	0	1	5	3
	Other colonies	0	2	36	30
	Total	(0)	(4)	(57)	(41)
9/1	Molds	0	2	7	2
	Staphylococcus	4	0	7	8
	Other colonies	0	1	7	12
	Total	(4)	(3)	(21)	(22)
9/2	Molds	17	8	160	120
	Staphylococcus	0	0	88	72
	Other colonies	11	7	0	16
	Total	(28)	(15)	(248)	(208)
	Grand total	35	37	498	488

windows were open. It is impossible to estimate the exchange of air in the open windowed, non-air conditioned rooms (742 and 743), but it is estimated to be many times that of the closed rooms. One is unable to note any significant drop in the pollen count in the rooms containing the air purifying apparatus as compared to those without it. In fact over 50 per cent of the counts were slightly higher in the rooms containing the air purifier.

Table III, Table IV and Figure 2 show the bacterial counts as obtained in each of the rooms. Again an obvious difference in counts between the closed air conditioned rooms, and the open non-air conditioned rooms can be noted. Though there was a marked fluctuation in bacterial counts from day to day, there was a constant reduction in the number of air borne bacteria and molds in the air conditioned rooms. When the rooms con-

TABLE IV. BACTERIAL AND MOLD COUNTS
(Filter Present in Air Conditioner)

	Contaminant	Room 740 Air Conditioned	Room 741 Air Conditioned and Puritron	Room 742 Open Windows	Room 743 Open Windows and Puritron
9/3	Molds	0	7	34	11
	Staphylococcus	0	0	4	0
	Other colonies	0	3	30	6
	Total	(0)	(10)	(68)	(17)
9/4	Molds	2	9	128	10
	Staphylococcus	0	0	2	0
	Other colonies	0	0	10	Innumerable
	Total	(2)	(9)	(140)	(10+)
9/5	Molds	0	0	0	0
	Staphylococcus	0	0	3	0
	Other colonies	0	0	4	0
	Total	(0)	(0)	(7)	(0)
9/6	Molds	0	0	8	20
	Staphylococcus	0	0	6	8
	Other colonies	5	1	8	12
	Total	(5)	(1)	(22)	(40)
9/7	Molds	0	0	14	10
	Staphylococcus	0	0	2	5
	Other colonies	2	2	22	35
	Total	(2)	(2)	(38)	(50)
9/8	Molds	1	0	10	7
	Staphylococcus	0	0	2	9
	Other colonies	2	0	35	48
	Total	(3)	(0)	(47)	(64)
9/9	Molds	6	15	3	4
	Staphylococcus	0	0	1	2
	Other colonies	5	13	Innumerable	Innumerable
	Total	(11)	(28)	(4+)	(6+)
9/10	Molds	5	8	2	3
	Staphylococcus	0	1	2	4
	Other colonies	11	4	38	Innumerable
	Total	(16)	(13)	(42)	(7+)
	Grand total	39	63	368+	194++

taining the purifier units were compared with the non-equipped rooms, it was impossible to detect any significant reduction in bacterial count due to the presence of this piece of apparatus.

CONCLUSION

A study was made to determine the effects of air conditioning and of an air purifying apparatus of the Puritron type on ragweed pollen counts and bacterial counts in a series of hospital rooms. The pollen counts and bacterial counts were significantly lower in the air conditioned rooms. The addition of a purifying apparatus caused no further reduction in either the pollen count or bacterial count.

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TREATMENT BY MEANS OF EMULSIFIED EXTRACTS OF SEVERE BRONCHIAL ASTHMA IN CHILDREN

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THE CHILD who is afflicted with chronic bronchial asthma, and who does not respond favorably to a program of conventional injections, is a problem. There are a number of methods of treating such disabled asthmatic patients. Corticosteroid hormones may be administered on a short or long-term basis, but the difficulties and dangers involved are too well known to need discussion. As an alternative, residential in-patient care in a rehabilitation center for asthmatic children may be suggested. Occasionally it is necessary to recommend psychiatric treatment because it is hoped that a psychic origin for the disorder may be unearthed. This paper describes seven severe asthmatic children treated with emulsified extracts. The span of time covered by the study was from November 1959 to the date of submission of this paper (March 1961).

The rationale, technique, quantity and treatment schedule of emulsion therapy are based on the recommendations of Brown.[1-7]

THE PATIENTS

All the patients had been subjected to the accepted traditional types of treatment (e.g., environmental controls, elimination diets, multi-visit injection therapy, et cetera) before being treated with emulsified extracts. For purposes of classification, the patient was considered to be suffering from severe asthma when wheezing occurred daily; when it had been present for several years, and had not responded to conventional desensitization procedures for a period of two years.

There were five boys and two girls whose ages varied from three to nine years. Before emulsified extracts had been administered, they had missed up to six-tenths of their school time. One six-year-old boy had been out of school 90 per cent of his school year. Before receiving treatment with emulsified extracts, forty-six courses of corticosteroid hormones had been given to these patients. While receiving traditional treatment, these patients had been hospitalized on twenty-seven occasions.

The children were treated with emulsified extracts containing those allergens to which they were clinically sensitive as well as skin test positive. All of the children were examined at intervals of one to three weeks.

THE EMULSIONS

Emulsions were prepared aseptically by mixing equal volumes of an emulsion vehicle and allergenic extracts. The emulsion vehicle was composed of nine parts of light liquid petrolatum NF No. XI (Drakeol 6 VR) and one part of an emulsifying agent, mannide mono-oleate (specially

treated Arlacel A, a non-ionic partial ester surface active emulsifier developed for use in emulsified vaccines of the water-in-oil type).

A satisfactory water-in-oil emulsion, as determined by microscopic examination, was prepared by the use of a Brown Emulsor.

THE EXTRACTS

Pollen extracts of trees (birch, oak, elm, maple), grasses (composed of equal parts of Timothy, June, red top and orchard), and ragweed, as well as alternaria and house dust, were furnished by Center Laboratories of Port Washington, N. Y.

CASE REPORTS

Case 1.—F. P., age six, an only child, developed asthma subsequent to an infection which occurred at the age of two. Continuous wheezing extended from his third year until the date of his initial visit. A traditional program of injections had been followed for three years. Flareups of asthma were noted after the ingestion of eggs and of shellfish. These were removed from the diet. A stay of six months in Florida was without effect. During November 1959, he received in a single dose, an injection of house dust, 2500 Protein Nitrogen Units (hereinafter referred to as PNU). During February 1960, he received an injection of birch pollen extract, 5000 PNU, and oak pollen extract, 5000 PNU both in a single injection and during March an extract composed of equal parts of Timothy, June, red top, and orchard grass pollens was administered in a single injection of 5000 PNU. On June 4, ragweed pollen extract, 5000 PNU was injected. During August he received his second injection of house dust extract, 2500 PNU.

Approximately six weeks following his initial house dust inoculation, improvement was observed. Subsequently, he required symptomatic medication, antihistaminic agents and bronchodilator drugs on only five occasions. Because of an upper respiratory tract infection, he missed only three days of school. This same patient had previously been absent from school more than 90 per cent of the scholastic year.

There has been a gain in weight of 10 pounds and in height of 2¼ inches. He is now in the fiftieth percentile for both.

Because he can now compete effectively in sports his personality has improved. He was an introverted, unhappy child. He is now well adjusted and relaxed and is interested in hobbies, sports and school.

Case 2.—R. R., age nine, had been treated by a traditional injection program since the summer of 1954 for perennial bronchial asthma and for pollinosis caused by the pollens of the trees, grasses and the weeds. His response to a traditional injection program was unsatisfactory. In July 1958, Prednisone was prescribed and was taken in a daily dose of 10 mg. Six months later, because of the development of a Cushingoid syndrome, no more was administered.

The patient, an only child (the second in the series) was the source of a great deal of anxiety to his parents. He was immature for his age and refused to cooperate in carrying out his medical program which included breathing exercises and postural drainage. Because of the increasing number of emotional problems, he was referred for psychiatric study and care.

During November 1959, he received his first injection of emulsified extract in the form of house dust, 5000 PNU. In March, birch pollen extract, 2500 PNU, oak pollen extract, 2500 PNU and elm pollen extract, 500 PNU were administered in a single injection. On April 4, he was given 5000 PNU of mixed grass pollen extract,

and on June 23, an injection of 5000 PNU of ragweed pollen extract was administered.

A summary of treatment with emulsified extracts indicates that the patient has had mild wheezing on only three occasions. For the past four months he has needed no medicines. Only five days of school were missed because of a viral infection. In the previous year, when he was receiving a traditional injection program, he missed forty days of school.

Although he has been under psychiatric treatment for over three years, his emotional problems have not changed.

Case 3.—G. P., aged seven, was first examined on September 19, 1959. Symptoms of asthma had first been observed when he was three. He had been treated by a weekly schedule of traditional injections for four years. Despite elimination diets and other therapeutic measures, his asthma remained unchanged.

The patient was emotionally disturbed almost all of the time. In addition, slight clumsiness was attributed to underlying brain damage. Because of his severe personality disorder, he has been under psychiatric treatment for three years.

In 1957, 1958 and 1959 he required oral corticosteroid hormones for status asthmaticus. In December 1958 and July 1959, he was hospitalized because of bronchopneumonia.

In November 1959, he received his first injection of emulsified extract—house dust, 2500 PNU. During February, birch pollen extract, 2500 PNU and oak pollen extract, 2500 PNU in a single injection, was administered. In June, he received ragweed pollen extract, 5000 PNU. During September, he received his second injection of house dust extract, 2500 PNU.

He wheezes now only one or two days each month and, generally, as a result of exertion. He has needed a Tedral tablet daily. Because of a virus infection, seven days of school have been missed.

Although behavior problems are present, there has been some improvement as reported by his parents and teachers.

Case 4.—G. M. was five years of age when first studied during July 1958. His allergic symptoms began at the age of three. His allergic bronchitis and asthma were not changed after injections of unemulsified extracts were administered for a period of two years. During December 1958, he was hospitalized for an infection, and, in 1958 and 1959 on seven separate occasions, he was treated with corticosteroid hormones for severe flareups of bronchial asthma.

It is interesting to note that when he received inoculations of unemulsified extracts, any dose which exceeded 2000 PNU of pollen extract resulted in large local reactions and in ten systemic reactions over a twelve-month period.

In November 1959, he received house dust in the amount of 1500 PNU. Alternaria extract (1500 PNU) was administered concomitantly and subcutaneously in the opposite arm. During February, he received a single injection of 2500 PNU of birch pollen extract, 2500 PNU of oak pollen extract and 2500 PNU of maple pollen extract. In April, he received 5000 PNU of mixed grass pollen extract and during June, 5000 PNU of ragweed pollen extract.

Approximately four weeks after his first injection of emulsified extract, improvement was noted. He has suffered three mild attacks of asthma during the past year. The first attack occurred in April, the second in July and the third in November.

He has missed ten days of school. During the previous year, he had been absent more than 70 per cent of the time.

Case 5.—N. M., aged seven, was examined in July 1959. She had been hospitalized on eleven occasions between the ages of two and six for treatment of asthma, asthmatic bronchitis and pneumonia. Injections of unemulsified extracts had been administered at weekly intervals for a period of four years.

The patient's mother had died of asthma shortly after childbirth. The child's father remarried in 1958. The stepmother could not effectively manage the patient's illness. The child was referred to a guidance clinic in 1958 and received treatment for more than one year. Psychiatric treatment was discontinued because the asthma was worse, and the behavior had not improved.

She was (July 1959) an underdeveloped, undernourished, scrawny seven-year-old girl. She appeared distraught, unhappy, and she cried easily. Her weight and height were below the third percentile. She was afflicted with pseudo-rickets.

During November 1959, she received her first injection of emulsified house dust extract in the amount of 2500 PNU. In April, 5000 PNU of mixed grass pollen extract was administered. In June, she received 5000 PNU of ragweed pollen extract. During September, a second injection of house dust extract, 2500 PNU was administered. At the same time, the patient received 1500 PNU of Alternaria in the opposite arm.

Approximately two months after her first injection of emulsified extract, there was noticeable improvement. During November 1960, she required epinephrine for a moderate attack of bronchospasm. On several other occasions, during periods of exertion, mild wheezing occurred.

Because her asthma is better, her appetite and sense of well-being have both improved. She has gained 10 pounds and grown 3 inches.

During the span of treatment, she has missed fourteen days of school. During the previous year when she had been treated with unemulsified extracts, she was absent more than 60 per cent of the school year.

Her personality and behavior have improved. There is at present no indication that she needs psychiatric study or care.

Case 6.—K. R., was three years of age when examined (July 1959). Her first attack of asthma had occurred subsequent to an infection in April 1956, when she was one year of age. There was continuous wheezing from her first to third year of age. She was hospitalized in July 1957, and again in August 1958, because of status asthmaticus. For the previous two years, she had been treated with weekly injections of unemulsified extract. Because of her continuous bronchospasm she was referred (July 1958) to a psychiatrist who reported that no psychic origin for her disease was discernible.

During November 1959, she was given a single injection containing 5000 PNU of house dust extract. In February 1960, 1500 PNU of Alternaria was administered. In April, the patient was given mixed grass pollen extract in the amount of 5000 PNU. During June, 5000 PNU of ragweed pollen extract was administered.

During the past year, two mild attacks of asthma, easily controlled by symptomatic medication, were experienced.

Case 7.—J. R., was eight years of age when examined in July 1959. He had suffered from continuous wheezing since the age of five. For the previous three years he had been treated by the traditional injection program.

Because of poor school performance and personality changes, he was examined in June 1958 by a psychiatrist who reported no emotional causes for his illness.

During November 1959, he received 2500 PNU of house dust extract. In April, mixed grass pollen extract in the amount of 2500 PNU was administered; during June 2500 PNU of ragweed pollen extract was given. He received his second injection of house dust (5000 PNU) in October.

The patient began to improve six weeks after his first injection of house dust extract and discontinued the use of any drugs for amelioration of symptoms. During the past year, he has wheezed on only one occasion and because of the mildness of the attack, no medication was needed.

During the period that he had been under treatment with unemulsified extract, he was out of school more than 40 per cent of the time. During the past year, however, he has missed no school.

RESULTS

It should be observed that in none of the patients were the results perfect. The children were, however, rehabilitated and their state was changed from being chronically disabled and severely asthmatic to what might be termed a mild bronchospastic state. It appears that hyposensitization with emulsified extract plays an important part in the treatment of allergic diseases.

EMOTIONAL DISORDERS

The relationship of asthma to emotional problems has been the subject of current reports.[8-10] Personality disorders had been present in all of the seven children, and they varied in degree from mild to severe. A child was classified as having a mild disorder when symptoms were not so serious as to need psychiatric treatment. Severely affected children were so classified when psychiatric supervision was deemed necessary. The following variants of personality, behavior or disposition were observed at one time or another in all seven children: fatigue, irritability, anorexia, emotional instability and unhappiness. When the patient improved, these symptoms, although not completely eliminated, were less often present.

Two of the children had suffered from severe emotional problems and had been treated by a psychiatrist before and during the time they received emulsified extracts. Their asthma lessened although their emotional problems were not changed. These two children demonstrate that, despite continued psychic stress, their asthma was less severe when they were treated with emulsified extracts.

SYSTEMIC REACTIONS

Systemic reactions were not observed in any of the patients treated with emulsified extracts. On the other hand, one patient (Case 4) who was treated with a traditional injection program had experienced ten systemic reactions during a twelve-month period when the quantity of unemulsified pollen extract exceeded 2000 PNU. In the hopes of lessening his disorder, attempts had been made to increase the quantity of unemulsified extract injected. Each experience with an unemulsified extract was, indeed, perilous. But more important, at the so-called tolerance level (2000 PNU), the patient's asthma was unchanged. By contrast, the same patient tolerated emulsified extracts in quantities of 2500 PNU to 5000 PNU, with no systemic reactions and with improvement. It appears that with the use

of emulsified extracts larger quantities of allergens can safely be injected. In addition, the immunologic level necessary for satisfactory clinical results can be reached, and the hazards of systemic reactions may be lessened if not completely avoided.

SUMMARY

During the years 1959, 1960 and 1961, seven severely affected asthmatic children who had failed to respond satisfactorily to programs of traditional injections were successfully treated with emulsified extracts of tree, grass and ragweed pollens and also with house dust and mold extracts. The quantities administered ranged from 1500 to 5000 PNU. Their severe bronchial asthma was modified so that they were only occasionally bronchospastic. The relationship of their emotional problems to their bronchial asthma was studied. When properly prepared and administered, emulsified extracts appear to be a safe and effective method for the treatment of bronchial asthma in children.

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WHAT MEN WILL NOT DO

There is nothing men will not do, there is nothing they have not done to recover their health and save lives. They have submitted to be half-drowned in water, and half-choked with gases, to be buried up to their chins in earth, to be scarred with hot irons like galley slaves, to be crimped with knives like cod fish, to have needles thrust into their flesh, and bonfires kindled on their skins, to swallow all sorts of abominations, and to pay for all this, as if to be singed and scalded were a costly privilege, as if blistering were a blessing, and leeches a luxury.—Oliver Wendell Holmes (1809-1904).

MUCOLYTIC THERAPY IN ASTHMA

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FOR OVER A CENTURY iodides have been used to ease expectoration in patients afflicted with asthma, bronchitis, and emphysema. This practice, although entirely empirical, has been so firmly established[1] that today the iodides remain indispensable or, at least, have not been replaced by a superior agent. This fact is particularly meaningful if one considers the unpleasant drawbacks associated with the iodides. They cause gastric irritation in many patients, and iodine sensitivity is frequently encountered. Many patients object to the taste of saturated solution of potassium iodide (SSKI), the usually prescribed form.

Apart from such more or less subjective drawbacks, iodides, although rapidly absorbed from the gastrointestinal tract, are also rapidly excreted via the lungs and kidneys, so that blood levels are maintained for a relatively short time. This is probably one reason why iodides are given in high dosage, often 100 times in excess of the normal body needs. It is conceivable that equally good expectorant action might be afforded with far lower dosage if effective blood levels could be maintained.

Recently, observations have been reported[2-5] concerning the efficacy of an organically-bound iodine preparation which would appear to have overcome, to a major extent, the drawbacks of conventional SSKI therapy.

We, ourselves, have used this form of iodine and feel that a review of our experience with its minimal effective dosage would be timely. I^{131} tracer studies indicate that it is metabolized slowly and maintains steady blood levels for several hours.[6] Moreover, this iodinated glycerol,* being stable in gastric juice, does not release iodine prior to absorption and causes no gastric irritation.[7]

Iodinated glycerol could be effective with a considerably lower iodide content than when SSKI is used as an iodide source. It had already been reported by Seltzer[8] that 125 mg/day of iodide provided by iodinated glycerol may take the place of about 2 gm of iodide per day provided by the 15-20 drops of SSKI t.i.d. usually prescribed.

In an attempt to further reduce this favorable 16:1 iodine ratio, we have tried to establish in our review the lowest daily dose of iodinated glycerol which would still produce the desired therapeutic effect.

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*Organidin,® the preparation used in this study, contains the iodinated glyceryl ether, iodopropylidene glycerol. We refer to the preparation as iodinated glycerol. Organidin was generously supplied for this study by Wampole Laboratories, Division of Denver Chemical Manufacturing Company, Stamford, Connecticut.

CLINICAL STUDY

The twenty-nine patients selected for this review all had bronchial asthma of many years' duration. One patient also had diabetes mellitus, and one had hypertension. Twenty-seven were men and two were women. The ages ranged from twenty-six to fifty-seven years.

TABLE I. MEDICATION OF PATIENTS BEFORE AND DURING IODINATED GLYCEROL THERAPY

Previous Therapy	Number of Patients Using the Medication	
	Before Iodinated Glycerol	During Iodinated Glycerol
Steroids	7	4
Ephedrine	24	7
Antibiotics	10	10
Isuprel	16	12
Antihistamines	3	3
SSKI	5	0
Tedral	3	5
Aminophylline	1	1
Ammonium chloride	4	2
Epinephrine inhalation	1	0

Subjective symptoms and objective findings were typical of long-standing bronchial asthma. All twenty-nine patients had a cough, which was productive of viscid yellowish-grey sputum in twenty-four. Dyspnea and wheezing were present in twenty-eight patients, but only one patient complained of pain in the chest. Objective findings were as follows:

Rales	9
Expiratory wheezes	27
Prolonged Expiratory phase	22
Hyperresonance	2
Rhonchi	3
Bronchovesicular breath sounds	1

Radiograph of the chest revealed emphysema in three patients and fibrotic changes of the lungs in one.

All patients in this group received a dosage of 30 mg iodinated glycerol, representing 15 mg of iodine, given four times a day along with the medications the patients had been previously taking.

Each patient was seen on the average of once a week for a period ranging from four to fifteen weeks, during which time the following notations were recorded:

(1) Expectoration—loose or tight, (2) Sputum—thin or viscid, (3) Dyspnea—better, same, or worse, (4) Presence or absence of audible wheezing, (5) Other medications used concomitantly, and (6) Side reactions, if any.

RESULTS

In each of these patients, a number of anti-asthmatic medications had been used with various degrees of relief. Significantly, during iodinated glycerol therapy, a considerable reduction in the need of these medications was noted. Table I lists the medications patients had been taking before and during iodinated glycerol therapy.

Of the twenty-seven patients receiving iodinated glycerol for four weeks or longer, two patients noted no change in their general condition, while the remaining twenty-five stated that they became less dyspneic, had less frequent asthmatic attacks, their sputum became less viscid, and they generally felt much better.

As is usually the case, not all patients remained available for continued observation; the data in Table II have therefore been kept limited to a six-week period.

TABLE II. SUMMARY OF RESULTS USING IODINATED GLYCEROL THERAPY

Symptom	Observations During First Visit	Observations During Last Visit
Expectoration		
Loose	5	25
Tight	24	4
Sputum		
Thin	5	21
Viscid	24	8
Dyspnea		
Improved	—	23
Same	28	6
Wheezing		
Absent	—	17
Present	28	12
Side effects		
None	—	27
Present	—	2

COMMENT

While our patients obtained obvious benefit from daily iodinated glycerol medication, it was our impression that maximum results were reached by the third week. Undoubtedly this reflects our low dosage. The generally recommended dosage is approximately twice as large and reaches full effectiveness within days.

It had, of course, occurred to us that influences other than medication might have been responsible for the observed improvement among this group of patients. In particular, the season of the year or other local conditions might have been a significant factor. A comparison with a number of patients selected as being comparable with the present group in environment, climatic conditions, and age—but who were not using any mucolytic-expectorant agent—showed no striking improvement in their condition during this particular period. Nor was there any noticeable change in those patients who continued their established potassium iodide therapy without deviation throughout this period.

Our patients were notably free from untoward reactions. Of the two patients who poorly tolerated iodinated glycerol, one had a history of duodenal ulcer and complained of gastric irritation, while the other, a hypertensive, used potent cardiovascular and diuretic drugs and complained of nausea.

CONCLUSIONS

1. Iodinated glycerol, when administered four times a day in doses of 30 mg, representing 15 mg of iodine, gave optimal results after two to three weeks of therapy. The results were noted as follows: (a) the patient felt improved; (b) the sputum became liquid and loose; and (c) asthmatic paroxysms appeared to be less severe and less frequent.

2. The above dosage was approximately one-half that usually recommended for more prompt response with iodinated glycerol. In this low dosage, iodinated glycerol continued to be beneficial when used over long periods of time.

3. There was a diminution of other medications on continued iodinated glycerol therapy.

4. No iodine intolerance was observed.

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USES OF EPIDEMIOLOGY

The main use of epidemiology is to discover populations or groups with high rates of disease, and with low, in the hope that causes of disease and of freedom from disease can be postulated.

Examples can readily be drawn from the riches of classical epidemiology. The observations on nutritional deficiencies (scurvy, goiter, beriberi, pellagra). The experience of peoples in relation to climate and season, "the epidemic constitutions of the atmosphere" (malaria; or pellagra), and to geographic and geological features (iodine deficiency). "Dangerous trades," and the industrial pulmonary diseases or the occupational cancers (epithelioma of the skin from cutting oils, and lung cancer associated with asbestosis are among the recent ones identified). The "unhealthiness of towns" (malaria, dysentery, pellagra, respiratory disease).—J. N. Morris. *Uses of Epidemiology*, E. S. Livingstone, Ltd., Edinburgh and London, 1957.

TREATMENT OF ASTHMA IN CHILDREN WITH ISOPROTERENOL SULFATE SUPPOSITORIES

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THE THERAPEUTIC EFFECT of isoproterenol sulfate suppositories was studied on a group of thirty asthmatic children,* ages five to fourteen years. Many types of allergic sensitivities and psychogenic problems were present in this group of children. Regardless of the etiology of their attacks, the children were treated with isoproterenol sulfate suppositories.

A comparative evaluation was made with the other types of suppositories used in this study. The types included were aminophylline[1] and glycerin placebo suppositories.

DESCRIPTION

Isoproterenol sulfate suppositories are a new form of Norisodrine® Sulfate in a cocoa butter base designed for rectal use. Isoproterenol sulfate is a synthetic amine possessing sympathomimetic properties. It is chemically related to epinephrine and ephedrine. This drug has a marked bronchodilating effect and has proved to be an effective agent in reducing bronchial spasm in asthmatic patients.[2] It has been shown to be more effective than epinephrine in overcoming bronchospasm, and it produces a significant increase in vital capacity and a marked relief from the dyspnea of asthma.[3]

MATERIALS AND METHODS

Thirty children participated in the investigation which was divided into two parts. The first was a subjective study in which the therapeutic effectiveness of the three types of suppositories was evaluated by means of observation and auscultation. The second was an objective study of the efficacy of these suppositories as demonstrated on kymograph tracings. The children in this study were also carefully observed subjectively, and these results were included in the subjective chart.

The dosage of the isoproterenol suppositories was arbitrarily set at 3 mg for children seven years and under, and 5 mg for children over seven years of age. The dosage of the aminophylline suppositories was 250 mg for children seven years and under and 500 mg for children over seven years.

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Norisdrine® Sulfate (isoproterenol sulfate) is a registered trademark of Abbott Laboratories, North Chicago, Illinois.

*Asthmatic Unit, Betty Bacharach Home, Atlantic City, New Jersey.

The severity of the asthma was determined by observation and auscultation and classified into three grades as follows:

1+ Asthma—Mild wheezing with no incapacitation.
2+ Asthma—Moderate wheezing with partial incapacitation. Child is ambulatory, has labored breathing and voluntarily restricts activity.
3+ Asthma—Severe wheezing with complete incapacitation.

Each asthmatic attack was classified as listed above prior to the insertion of either the isoproterenol suppositories, the aminophylline suppositories or the glycerin placebo suppositories. The asthmatic attack was again classified in forty-five minutes and repeated in one and one-half hours. The same observer noted the results in every instance. The results are listed in Table I.

TABLE I. COMPARATIVE STUDY OF THE EFFECT OF ISOPROTERENOL, AMINOPHYLLINE AND PLACEBOS IN SUPPOSITORY FORM ON SEVERE ASTHMA IN THE PEDIATRIC AGE GROUPS

Subjective Study

3+ Asthma (Initial Evaluation)

	Results at End of 45 Minutes			Results at End of 1½ Hours		
	Isoproterenol	Amino	Placebo	Isoproterenol	Amino	Placebo
Number of attacks	43	21	2	43	21	2
2+ or 1+ asthma	32	12	2	23	12	2
Complete relief	9	8	—	18	8	—
No effects	2	1	—	2	1	—

2+ Asthma (Initial Evaluation)

	Results at End of 45 Minutes			Results at End of 1½ Hours		
	Isoproterenol	Amino	Placebo	Isoproterenol	Amino	Placebo
Number of attacks	24	9	1	24	9	1
1+ asthma	17	4	1	9	3	1
Complete relief	6	4		14	5	
No effects	1	1		1	1	

The objective study was done by using a pneumatic rubber chest cuff attached to a writing kymograph. A two-minute control tracing was taken before the suppository was inserted. Tracings were made every five minutes for forty-five minutes. These tracings demonstrated the bronchodilating effect of the three types of suppositories (isoproterenol, aminophylline, and the glycerin placebo). The severe asthmatic attacks showed an irregular rate with deep, irregular respiratory excursions. The bronchodilating effect was demonstrated by the change to a slow regular respiratory rate and a decreased, even respiratory excursion.

A subjective evaluation of the severity of the asthmatic attack was made in each of these children at the end of forty-five minutes and then again in one and one-half hours. The results of this objective study may be seen on Table II.

RESULTS

Sixty-seven attacks of asthma were treated with isoproterenol suppositories. In sixty-four asthmatic attacks (96 per cent) there was an improvement at the end of forty-five minutes. Only three patients, or 4 per cent, showed no improvement.

Of the forty-three asthmatic attacks that were classified 3+ and the treatment was with isoproterenol suppositories, thirty-two showed marked relief at the end of forty-five minutes, while nine showed complete relief. In only two was there no relief. When the children were observed for one and one-half hours, the results were even better. Eighteen of these forty-three asthmatic attacks subsided completely, and in twenty-three others, there was measurable improvement. The average duration of the relief was five and one-half to six hours.

TABLE II. COMPARATIVE STUDY OF THE EFFECT OF ISOPROTERENOL, AMINOPHYLLINE AND PLACEBOS IN SUPPOSITORY FORM ON SEVERE ASTHMA IN THE PEDIATRIC AGE GROUPS

Objective Studies with Kymographic Tracings

3+ Asthma (Initial Evaluation)

	Results at End of 45 Minutes			Results at End of 1½ Hours		
	Isoproterenol	Amino	Placebo	Isoproterenol	Amino	Placebo
Number of attacks	9	5	2	9	5	2
2+ or 1+ asthma	6	2	2	4	2	
Complete relief	2	2		4	2	
No effects	1	1		1	1	

2+ Asthma (Initial Evaluation)

	Results at End of 45 Minutes			Results at End of 1½ Hours		
	Isoproterenol	Amino	Placebo	Isoproterenol	Amino	Placebo
Number of attacks	4	—	—	4	—	—
1+ asthma	2	—	—	1	—	—
Complete relief	2	—	—	3	—	—
No effects	0	—	—	0	—	—

Treatment with aminophylline suppositories was evaluated in the same manner. The results of treatment with isoproterenol suppositories were as good as those obtained with aminophylline suppositories both in forty-five minutes and at the end of one and one-half hours. The average duration of the relief with aminophylline was four to four and one-half hours as compared to the five and one-half to six hours relief obtained by the isoproterenol suppositories.

The results of treatment with the placebo suppositories showed their lack of effectiveness.

Chi Square values for four parts of Table I, and two parts of Table II are presented. In these calculations, placebo data were not used. Thus, the values of Chi Square test the hypotheses that isoproterenol and aminophylline are equally effective under different conditions of measurement. In each of the six tables, the conclusion is that there is no statistically

significant difference in effectiveness. The calculated Chi Square values are as follows:

Degree of Asthma		*Subjective*	*Kymographic*
3+	45 minutes	2.18	.93
	1.5 hour	.08	.207
2+	45 minutes	2.05	
	1.5 hour	.55	

A Chi Square value of 7.81 would be required for significance at the 5-per cent level. Thus, the calculated values are not close to a significant difference.

The results of the objective study with kymographic tracings showing the gradual recovery from the attack of asthma following the insertion of the isoproterenol or aminophylline suppository were similar to the results obtained in the subjective study. The interpretation of the tracings was discussed under the section entitled "Materials and Methods." The objective study confirms the findings of the subjective study.

SIDE EFFECTS

No toxicity or side effects were noted during treatment in the sixty-seven attacks of asthma utilizing isoproterenol suppositories for treatment. One boy developed a tachycardia with a heart rate of 120 per minute; he was treated with the same type of suppository on three other occasions without developing a tachycardia. The tachycardia developed when the suppository was first used; moreover, it was his first experience with a suppository. Inasmuch as he failed to develop a tachycardia on three other occasions when isoproterenol suppositories were used, it may be possible that his tachycardia resulted from nervousness.

While aminophylline toxicity has been reported[4-5] with the use of aminophylline suppositories, none occurred during this study.

CONCLUSIONS

1. Isoproternol suppositories in appropriate dosage is a safe and effective means of relieving an asthmatic attack.
2. Isoproterenol suppositories were as effective as the aminophylline suppositories in relieving patients in attacks of asthma, but the therapeutic effect was more prolonged. The average duration of the effects of isoproterenol suppositories was five and one-half to six hours, while that of aminophylline suppositories was four and one-half to five hours.
3. Isoproterenol suppositories showed no toxicity in this study.

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ALLERGIC RHINITIS AND BRONCHIAL ASTHMA—TREATMENT WITH PARENTERAL METHYLPREDNISOLONE ACETATE

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INTRAMUSCULAR methylprednisolone acetate (Depo-Medrol) reportedly is well tolerated and clinically active for approximately one week.[1] Indirect blood level measurements suggest that it may be active for even longer periods. In adult women with the adrenogenital syndrome, the injection of 80 mg methylprednisolone acetate suppressed 17-ketosteroid excretion for two to three weeks. In children with the adrenogenital syndrome, the injection of 40 mg had the same effect.[2]

The availability of such a steroid preparation increases the physician's ability to control his patients because he is assured that the prescribed dose will be taken. None will be put aside for future use with present inadequate control of symptoms, and the dose will not be exceeded nor the period of treatment prolonged. The latter is particularly important in asthma, because prolonged treatment of this disease with corticosteroids may be hazardous.[3-6] In addition, this type of preparation may be useful during periods of investigation, for symptoms may be controlled with adrenal steroids without interfering with skin tests.[7,8]

The present study was undertaken for three reasons: (1) to determine the efficacy of parenteral methylprednisolone acetate in the treatment of hay fever and asthma, (2) to prevent patients from prolonging or otherwise altering steroid dosage, and (3) to see if allergy skin tests remain useful in the investigation of patients whose symptoms are controlled with parenteral methylprednisolone acetate.

MATERIALS AND METHODS

Twenty-six children, ranging in age from two months to thirteen years, a youth aged nineteen, and two adults, ages forty-three and forty-five, were treated with an aqueous suspension of methylprednisolone acetate. Nine patients were female; twenty were male. All were seen during the ragweed season, 1959, and each had severe respiratory allergy suitable for steroid treatment. Six patients had bronchial asthma only, eleven had bronchial asthma and allergic rhinitis, and twelve had allergic rhinitis only. These were complicated by urticaria in two instances, eczema in one, and secondary infection in two.

Each cubic centimeter of the suspension employed contained methylprednisolone acetate 40 mg, polyethylene glycol 4000 30 mg, and a pre-

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servative, myristyl-gamma-picolinium chloride, 1:5000. Injections of 0.5 to 2.5 cc were made deep in the gluteus maximus muscle.

Doses for children were calculated to supply approximately one mg of the steroid per pound of body weight. Adults received doses of 80 and 100 mg. Three patients required a second dose, but all others received only one injection.

Previous allergy studies had been made in most patients, and studies were done during the period of treatment in three patients.

If satisfactory control of symptoms and signs occurred, the response to treatment was considered to be good. Other responses were rated poor.

TABLE I. SYMPTOM CONTROL FOLLOWING INJECTION OF METHYLPREDNISOLONE ACETATE

Diagnosis	Number of Patients	Response	
		Good	Poor
Asthma	6	6	—
Asthma and allergic rhinitis	11	10	1
Allergic rhinitis	12	9	3
Totals	29	25	4

RESULTS

Patient responses are summarized in Table I.

Of the four patients with a poor response, it seemed in retrospect that two probably received an inadequate dose. The third developed urticaria on the day following her injection, and the fourth initially reported improvement, but three days later denied it.

The time of onset of relief after injection varied: in one instance it was immediate, in many it was prompt, occurring within the first few hours, and in a few it was complete only after twenty-four hours. Usually, partial relief was present within four hours, and complete relief within twelve hours.

Many patients treated with one injection experienced no return of symptoms during the remainder of the ragweed and fall mold season. In those patients whose symptoms recurred, relief following a single injection of methylprednisolone acetate varied from two to fourteen days. Relief usually lasted for seven days.

Patient acceptance was excellent, and no side effects occurred.

CASE REPORTS

Case 1.—A two-year-old boy, weighing 28 pounds, seen on August 31, 1959, had a history of asthma every week or two since May. Diagnosis after physical examination was flexural eczema, allergic rhinitis, and asthma. On October 1, 1959, he experienced another attack of asthma and received 40 mg of methylprednisolone acetate intramuscularly. Symptoms were somewhat relieved within two hours and were adequately controlled during skin tests and the initiation of definitive allergy

treatment. When seen on October 13, 19, and 27, there was no evidence of rhinitis or asthma, and the eczema was improved.

Case 2.—A two-year-old boy, weighing 24 pounds, seen on August 29, 1959, had experienced intermittent asthma for two months. He was treated with ephedrine, potassium iodide, and an antibiotic agent. Skin testing was postponed because he was taking ephedrine. On September 3, 1959, his asthma became more severe, making him acutely ill. He received methylprednisolone acetate 20 mg intramuscularly. This injection controlled symptoms and made it possible to discontinue ephedrine, do necessary skin tests, and initiate definitive therapy before symptoms recurred.

Case 3.—A six-year-old boy, weighing 40 pounds, seen on October 30, 1959, had severe asthma. Symptoms improved within an hour following an injection of methylprednisolone acetate 40 mg intramuscularly. Indicated skin tests were then made. Symptom control continued following the injection of methylprednisolone acetate until the initiation of definitive management.

DISCUSSION

The results of this study favor single intramuscular injections of methylprednisolone acetate in managing acute respiratory allergy on three counts: excellent symptom control, patient acceptance without pressure for repeat doses for the control of mild symptoms, and the successful use of skin tests while the patient's symptoms are under control.

Frequently impressed with the results of treatment with oral steroids, patients want to continue taking them, even if symptoms are mild. Unaware of the dangers associated with prolonged treatment, they ask their doctors for refills or even seek refills from pharmacists. When these efforts are successful, the physician loses control of his patient. Sometimes this loss of control is not realized until the patient is in extreme danger. For instance, a patient seen by one of us (H. A.) for allergy testing had been maintained on corticosteroids for a long period. After the steroids had been briefly discontinued, she became refractory to them. As we learned later, she died in status asthmaticus while being treated with massive doses of steroids.

In the present study, no patient asked for additional steroid therapy. All patients readily accepted physician control assured by the use of a medication requiring parenteral administration.

We believe that intramuscular methylprednisolone acetate is indicated in the treatment of acute allergies, especially in the ragweed season. The seven to ten-day period when pollen counts attain their highest values in our area, is most critical because, at this time, symptoms often occur in patients ordinarily well controlled by usual allergic management. With a single injection, a patient can be given immediate, or almost immediate, relief that lasts through this critical period of exposure. For small children who refuse to take medicine, intramuscular methylprednisolone is ideal—they cannot reject it, and one injection will give relief for a week to ten days or longer.

When sympathomimetic agents and antihistamines are used to control allergy symptoms, false negative skin tests may occur. Therefore, definitive therapy often is postponed for long periods in patients with severe symptoms. When corticosteroids are used, on the other hand, skin tests are not affected. In three cases reported here, responsible antigens were determined through demonstration of positive skin tests, and treatment with appropriate extracts was started during the period of symptom control following a single injection of methylprednisolone acetate.

SUMMARY AND CONCLUSIONS

Twenty-nine patients with asthma or hay fever were treated with intramuscular methylprednisolone acetate in doses of 20 to 100 mg. In twenty-five patients, symptom-relief was good, lasting on the average seven days after one injection. Patient acceptance was excellent, and therapy did not interfere with necessary allergy tests.

It is concluded that intramuscular methylprednisolone acetate is particularly useful in two situations:

1. Acute allergic episodes in which treatment with medication entirely under the control of the physician is desirable.
2. Severe allergic states in which symptom control is needed during the allergy workup.

ADDENDUM

Approximately thirty additional patients received parenteral methylprednisolone acetate during the 1960 ragweed season. Only one patient had an unsatisfactory response. No side effects occurred.

ACKNOWLEDGMENTS

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RAGWEED POLLINOSIS

A Definitive Study of 1501 Patients Treated by Means of One Annual Injection of Emulsified Pollen Extract (XIII)

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ALLERGY TO RAGWEED POLLEN can at best be labeled a misery of mankind. The damage it does is beyond assessment. There are the inability and the incapacity for work or play because of the itching of the eyes and of the nose, the tears, the sneezing and the large amounts of nasal mucus. In some patients the pruritus, which affects the palate or else the internal ears, or both, is intolerable, and in others the cough and the wheeze vary from occasional breathlessness to severe asthma, for which the patient must be treated—often in a hospital for as long as seven to ten days. And how are to be measured, for the mildest afflicted patients, the holidays missed; or for the most severely affected, the costs of treatment? Few patients die. How many wish they could!

What can the patient do to avert his misery? Gravel, taken six feet deep, is indeed a counsel of despair. Flight? To wherever necessary, and for as long as six or more weeks is beyond the means of many, should their type of work permit so extended an absence for those who needs must be with their families or else must work in offices. Injections? How many, and for how long a time, and at what cost in how much time taken, effort expended or money spent?

The hypodermic syringe is not the most pleasant of objects however calmly the patient contemplates the preparation of his "cocktail." The injection, often immediately painful and sometimes followed by a swelling, is less easily tolerated. The only-too-often swollen arm of limited use to the patient is neither lightly accepted nor cheerfully endured, although the patient may not voice his complaint unless the disability becomes truly intolerable. And what of the ever-present fear or actually incurred systemic reactions? These force many patients, after they have suffered one or two—or, with fortitude, have endured three or four—to decide that the disorder is the lesser of two evils.

The results, were they consistently good, would be worth the effort involved, but—although the patient who reports late or irregularly may be chided and the symptoms he suffers blamed on his lack of attendance or short period of treatment—what is to be said to the others who report and, be it said, cheerfully week after week and follow all of the "rules," and yet

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cheerlessly are no better or so little improved? We can only say that had they not taken the courses of injections, they might have been worse. The continued loyalty of such patients is a tribute of their faith in their physicians and not a measure of the value of the method of treatment.

The immunologic picture is, if anything, more dismal. The case for the multiple injection courses of treatment cannot be said to have been proven. That there are groups of patients who do take the injections, and as a consequence are better than are other groups who do not subject themselves to the same type of treatment, is a matter of everyday observation. This thought has kept many allergists in practice. But how much better and why? How are differences of improvement, when short either of complete success or of failure, to be measured? The means have not as yet been invented.

The reaginic response may increase, decrease or be unchanged. Blocking antibodies (Type III) may increase or decrease, and in many patients may, for one year, parallel the clinical picture, and for the next be completely diverse. Hemagglutinin titers cannot only be raised non-specifically, but may be seen in patients "treated" by placebo injections. Provocative tests do come closer to the natural patterns of response, but when they are done once or twice and pre-seasonally, how far distant they are indeed from the varying but continuous day-to-day exposure which grinds the patient down. When they are done co-seasonally the amount of pollen or pollen extract we use must always be added to that to which the patient has been exposed. This pollen differs in the quantity deposited on the mucous membranes and is not parallel to the amount or the rate of absorption. It can never be the same for any two patients and is beyond measurement in any one.

There is no doubt that in animals and in man, an injection of pollen extract results in an antibody. It can be produced, and in large amounts, by normal non-allergic subjects who did not at the time need it and in whom an allergic clinical response cannot, by these means, be said to have been prevented. After all, one cannot make a subject who is not allergic less allergic. What we do is quite different from what happens when we take a patient who will be exposed to small pox and by vaccination make it difficult for him to become afflicted. Until the relationship of the antibody response of the allergic patient can be proven to be quantitative and can be used to anticipate who will or will not be burdened by pollinosis during the ensuing season, the means of proving its presence, however subtle, strongly resembles the more complex methods of playing Solitaire. In the present state of medical knowledge none of the studies so far reported upon are meaningful as regards an actual patient.

A long cold look at the treatment of pollinosis lets us see other demerits which time and custom alone have led us to accept. In New England the patient is, at the most, afflicted for six to ten weeks. He needs no protection for the remaining forty weeks of each year, and yet by the administration of pollen extract, we expose him to pollen one way or another for all of fifty-two weeks, and often several times each week. We say that we must

do this to enable him to benefit from what the injections supposedly do. But do not the injections of small amounts of extract given during the symptom-free period affect the patient adversely? His first comment after he has been changed to the enapothetic types of injection is that he feels so much better during the time when he receives no injections. In other words, he enjoys his painless injection, the absence of consequent discomfort and a sense of well being. The perennial type of post-injection general malaise was, once upon a time, termed a "protein hangover." The patient was not always conscious of its presence in minor degrees until he was free of it.

We have not been derelict in our duties to our patients when we have subjected them to multiple visit programs of treatment, because these appeared to represent the best we knew. But a great many of us were as unhappy as were our subjects of immunologic exploration. There were many suggestions as to how our methods of treatment might be changed.

Some allergists sought and emphasized the factor of safety. They administered small quantities of extract for extended periods of time. After all, the only truly safe injection of anything is that which no one administers to anybody for any disorder. The act itself is irretrievably irreversible. Once placed into the tissues, the extract stays put, and no one can withdraw it with his syringe and be happy that it is once more in his possession. Others, granted the inconveniences of reactions, accepted them as a necessary evil. If a small number of these were, in any case, inevitable, why not ignore them and perhaps by larger quantities of extract injected for longer periods of time, attempt to achieve more perfect results? Their patients received what we now know to be tremendous amounts of extract, and usually within a framework of twenty to forty injections. A third group of allergists combined the two types of programs, and their patients received injections which consisted of doses not so great, but given perennially and for year after year.

Other allergists attempted to avoid the reactions which followed injections by a change of the site treated. There was a spate of intranasal sprays, nebulized extracts and of intracutaneous inoculations. These resulted in extraseasonal symptoms as well as some experienced seasonally. Extracts and whole pollen were both taken orally. The itching of the eyes or nose was transferred to another organ, the treatment of which was, if anything, more complex and, in our civilization, somewhat embarrassing. The reports in such cases were often encouraging. The patients frequently changed allergists.

At the hands of yet other allergists it was not the program of injections or the site of treatment which was the object of scrutiny, but rather the substance used. Everything that could imaginably be done to pollens or to their extracts was done. None lacked merit but few possessed much. Those of these manipulations which were only too often associated with the most denatured antigen were safest as regards systemic reaction. With some

particular types of denaturalization there were not only local nodules, but, unfortunately, the poorest results. Safety purchased at the cost of residual symptoms was not satisfactory except to those to whom the so-called safety precautions were important to a point beyond that which was needed. They preferred the uncertainty of amelioration for the certainty of complete suppression of the signs and symptoms of pollinosis.

After all, the only two important factors are safety and success. There are truly no others. Safety can be insured, and obtained by the release of an extract so slowly that the body of the most allergic patient will not be exposed to a quantity beyond his "tolerance." The total amount injected can be so great that the patient who needs it most, although exquisitely sensitive, will not be penalized by either a multitude of injections or by local or general reactions.

For pollen extracts, an emulsion is obviously the ideal form of administration, because the physician may use an extract as undenaturalized as is possible and yet control the rate of release and within narrow limits. It is interesting to note, in passing, that as early as 1938, the author published in the Letters of the International Correspondence Club a method of preparing an emulsion of epinephrine in oil[1] for effective and immediate, but also for prolonged absorption time.

There are two reasons why emulsions of extract are not as popular as their qualities and properties suggest they might be.

First, the rate of absorption of extract so prepared depends on the preparation of a suitable type of emulsion. When the droplets are large, the release is immediately rapid, and the coalescence of the droplets of different sizes results in a total increased absorption rate which defeats the chief purpose of the enapothetic type of injection. It is not at all surprising that there are patients who do not tolerate such treatment, which only superficially resembles the true opsiphylactic method of achieving protection. When the droplets vary greatly in diameter, then for electrochemical reasons they coalesce more rapidly and the emulsion cracks. In such cases, all of the contained extract is immediately absorbed and what appeared to be an emulsified extract proves itself by its immediate effects to have been quite otherwise.

Second, the composition of the continuous phase determines the type of emulsion and also its rate of absorption. The animal and vegetable oils are, in their own right, assimilated so quickly that in few patients can the release of the contents of the droplets be slowed to a sufficient degree to warrant the preparation of an emulsion of the extract used. The patient suffers his systemic reaction as soon as he turns the corner. The investigator, in blissful ignorance, reports a low reaction rate and especially when the patient is, by definition, labeled as a "reactor", and only one of the many reactions is listed for "statistical" purposes. Some investigators play games. When the patient reacts, it is said that he has been wrongly classified as to dose and the reaction is ignored. Whenever the patient does not react

systemically, then the emulsion is labeled as satisfactory, no matter what the size of the droplets of extract.

Mineral oil is an ideal menstruum. Those physicians who were not familiar with its history fear that it may possess untoward effects. All experimental studies prove it to be harmless.

The problem can be solved by means of mathematics. The ideal droplet size may so be determined. The number of joules needed to exert the necessary shearing force and to convert the kinetic energy involved into droplet surface charges is measurable. Emulsion chemistry points the way to methods of preparation so that the rates of extract release can be predetermined and almost exactly. We can prepare emulsions consisting of two oils, of which one was, but did not need to be, mineral oil, with two emulsifying agents, of which one was the now familiar mannide-mono-oleate (Arlacel A, Atlas Powder Co.), and with an added stabilizing agent which, with one of the two emulsifying agents, maintained the allergenic potency of the extract used. Would the clinical results prove the basic considerations to have been correct? They did!

The thirty or more studies in press or in preparation merely reflect the results of maturity of thought and of improvements in methods. Each is not a hitching post but a guide post. That the emulsified extracts did what they were supposed to do, there was no doubt. But in what quantities, in whom, and how well, and when to be given could not be determined, with any greater exactness than that which characterizes the practice of clinical medicine, and that is, in the crucible of actual experience.

In this regard it should be realized that the allergic disorders are characterized by qualitative as well as by quantitative states. An allergic patient, although free of symptoms, differs qualitatively from a non-allergic control. Once allergic, however, body changes objective in nature may be measurable although the patient suffers from no subjective symptoms. Equally often the patient is obviously allergically ill, but there are no so-called objective or laboratory measurements of degrees of discomfort. How does one "prove" the presence of a food-induced headache or measure the amount of either the discomfort or of the pain involved? An examination of any quantitative studies of any aspect of allergy, beginning with tests and ending with "statistics" which purportedly tell us that the results of this or that type of treatment were "significant", makes us wonder what has happened to our sense of humor.

Because no one has, as yet, devised a means of measuring what is involved in an itching palate or an intolerable tickle of the upper nasal passages, there is no choice. The patient must be made objectively and subjectively well. He will seek subjective freedom from discomfort. Our standards are always higher than his. We seek to give him such subjective states of comfort, but when possible (as by pulmonary function studies of asthmatic patients), there is objective proof of restoration of physiological integrity. Is it not strange that we cannot prove how sick a sick patient may be

and yet need no proof of the obvious fact that he is free of illness? What has so far been written may be termed the purpose of the present study.

TABLE I. THE PATIENT POPULATION DISTRIBUTED ACCORDING TO AGE AND SEX

Years	3-5	6-10	11-20	21-30	31-40	41-50	51-60	61-70	71-77	Total
Males	13	74	256	145	153	130	54	35	11	871
Females	6	35	134	110	153	110	59	19	4	630
Total	19	109	390	255	306	240	113	54	15	1501

Comment (Table I).—The patient population, as distributed by age and sex, is shown in tabular form and needs no comment.

TABLE II. THE NUMBER OF PATIENTS DISTRIBUTED ACCORDING TO DISORDER AND DURATION

Years	1-10	11-20	21-30	31-40	41-50	51 or More	Total
Number of patients with bronchial asthma	171	121	42	28	10	6	378
Number of patients with allergic coryza	340	284	134	52	17	6	833
Number of patients with bronchial asthma and allergic coryza	108	81	50	27	4	0	270
Number of patients with other disorders	10	6	4	0	0	0	20
Total	629	492	230	107	31	12	1501

Comment (Table II).—From the second table, which lists the patients in accordance with their chief disorders, it may be seen that 833 suffer from simple "hay fever," and that almost 500 had been afflicted for more than ten consecutive years. This same duration of the disorder is also true for the more than 200 asthmatic patients and of 150 others whose histories proved them to respond to pollen with signs and symptoms affecting all of the respiratory tract.

The remaining twenty patients reported for treatment because exposure to pollen was followed by such limited responses as allergic conjunctivitis, tracheitis, pharyngitis and, in several patients, seasonal exacerbations of urticarial or eczematous disorders.

TABLE III. THE NUMBER OF PATIENTS DISTRIBUTED ACCORDING TO SKIN TEST REACTIVITY

Testing Solution in P.N.U./ml	P.P.P.*	+100	+1000	+2000	+4000	+10,000	+20,000	Not Skin Test Reactive	Total
Number of patients	601	179	173	344	171	26	4	3	1501

*P.P.P. refers to positive responses to pressure puncture (scratch test).

Comment (Table III).—At no time has any relationship between the size of the skin test response and the degree of clinical sensitivity been

measurable in any one patient, although generally the larger test responses are more frequently noted in those who are more "allergic." There are so many exceptions to this so-called test of sensitivity that the size of the skin reaction is a fragile a reed as it is possible to lean upon. This is especially true when the repetition of the skin test evoked by the scratch test method is no larger when the patient is titrated "upwards", that is, by stronger concentrations used intracutaneously.

The table is published for what it is worth. One might conclude that 601 patients were extremely sensitive because large reactions followed the application, for a pressure puncture test, of a drop of 10,000 P.N.U./1.0 ml solution to the skin. It could equally well be said that 171 patients were so insensitive that it took intradermal contact with 0.02 ml of a 4000 P.N.U./1.0 ml solution of extract to evoke a positive reaction. Neither conclusion is warranted.

As the studies progressed, tests with the more dilute solutions were omitted excepting in those patients who were referred, but only because of the many systemic reactions which had previously followed injections of unemulsified extract. There is a certain irony in the fact that allergists are so far from labeling the enapothethic type of treatment unsafe that they prefer to use it for their most sensitive patients! Interest was, for other patients, centered only on whether the skin did react. It was in every case known that the patient was actually allergic to ragweed pollen. This clinical fact could be established beyond doubt. That they showed positive skin test reactions was interesting but not particularly pertinent.

Other patients whose allergy has been determined by means of other types of tests have also been treated, but the injection procedures to be used for skin test negative patients will be the subject of a separate report. In approximately half the number of patients who had previously been tested, the skin test response, as measured by titration techniques, did not change, although the treatment had been successful. In approximately one-fourth of the patients the test reaction diminished, and in the other fourth it increased. It is obvious that, had any of these patients gone to another physician, the reactions evoked by his tests would have told the second physician nothing of the patient's "immunologic" state.

The twenty-six patients who are listed as reacting to 10,000 P.N.U./1.0 ml tests, and the four who similarly gave positive reactions when the skin was challenged with up to a 20,000 P.N.U./1.0 ml solution of pollen extract are included because they represent cases in point. All were clinically allergic. Almost all had been treated for "intrinsic asthma." None had been given injections of ragweed pollen extract, but all had reacted to the presence of the pollens in the air, and on the same dates and to the same degree as had new and untreated ragweed pollen allergic patients, as proven by symptom diaries, and by personal observation. They had in the past been permitted to go untreated because there was no "proof" of pollen sensitivity. These criteria were also true of the three patients listed as not

at all skin test reactive. All responded to treatment.

It should be noted that they are not ever treated only on the basis of a positive test response, but because they are truly distressed by their pollinosis. No skin test positive patient is not pollinotic. The few skin test negative patients were, indeed, pollinotic.

The skin test reactions are obviously looked upon, as noted, as a general qualitative indication of sensitivity. They need not be present. The practice of using them as a quantitative standard has been abandoned. Although I reported that I so regarded them, I have never at any time truly believed that they indicated the degree of a patient's sensitivity. It is indeed difficult to divest oneself of the heavy and smothering mantle of so-called authority.

The conjunctival type of test is also no longer in use because it tells us nothing either quantitative or qualitative. Each of the two separate studies of these types of tests has for some time been in preparation for publication. They are not in print only because priority has been given to the more illuminating aspects of the opsiphylactic type of treatment, and especially the clinical results, which any one who uses a properly prepared emulsion of extract can duplicate.

TABLE IV. THE DOSES OF EMULSIFIED EXTRACT ADMINISTERED AND THE NUMBER OF PATIENTS TREATED WITH EACH

Dose (P.N.U.)	250	500	750	1000	1500	2000	2500	5000	7500	10,000	Total
Number of Patients	7	45	1	55	20	2	421	424	46	480	1501

Comment (Table IV).—Although the fourth table resembles others published in these studies, it differs from them in that it represents again an increasing maturity of thought as regards the treatment of allergic patients. The earlier tables attempted to follow a tradition powerful in its pervasion of all of our thinking and, only too often, it set aside the history of the patient so that the skin test reaction and the dose administered could be related. This attitude was also a projection of the past into the future as though an injection of emulsified extract were a modification of the traditional multiple visit method of treating a patient excepting for a reduction in the number of injections. There is in this type of reasoning neither logic nor truth.

The patient's dose depends only on the clinical factors involved as determined by his history; on the date he reports for treatment; on the amount of exposure anticipated, and on the site of the injection chosen. As an example, let us see how a hypothetical patient may be treated. Although no such entity as a hypothetical patient exists, there is no reason why one may not be discussed.

Let us suppose that the history is one of moderate symptoms, beginning late in August, and ceasing by early October. Should the patient report during May, an injection of 10,000 P.N.U./1.0 ml is administered, in

this instance, subcutaneously. But, should the same patient have been referred for his injection during the first week in August, it is obvious that he would have needed more rapidly induced protection, and that whatever protection is afforded him is for the months of September and early October. In other words, he needs less and he needs it now. He would probably receive 5000 P.N.U./0.5 ml injected intramuscularly so that absorption may be more rapid in accordance with the total number of units contained in a lesser quantity of emulsion and because of the site of deposition. In other words, on the basis of an injection of 0.5 ml as compared to 1.0 ml, the extract will be absorbed at least four times more quickly. To this speedy but safe absorption will be added the quick effects due to intramuscular as compared to subcutaneous injection.

Should the same patient again have reported when symptoms were present, and during the last week of August or the first week of September, the amount injected would be 1000 P.N.U./0.25 ml, also placed intramuscularly. Treatment for symptoms would probably be needed for ten days. In the absence of an injection, the patient would probably, as evidenced by his history if it be dependable, suffer for all of the length of the pollen season.

Let us take as another example a patient of great clinical sensitivity who had never, ever received an injection of any pollen extract. Were he to report for treatment sometime during May, his first dose might be as little as 250 P.N.U./0.5 ml placed subcutaneously. A second injection of 2500 P.N.U./1.0 ml might be injected and again into the subcutaneous tissues sometime during June and then either 5000 or 10,000 P.N.U./1.0 ml (subcutaneously) during July. But, were he to plan to take his vacation for the three weeks represented by the last week in August and the first two of September, no third injection would be needed because it obviously would not be necessary. Should it be difficult or impossible for him to return for a second or a third injection, then the first would comprise a total of 2500 P.N.U./1.0 ml and the patient informed that he might suffer some minor difficulty. But then again, he might not!

Of the 1501 patients studied as regards the present or sixth type of emulsion used, 1325 received, without reaction, either 2500, 5000, or 10,000 P.N.U. of ragweed pollen extract. None was treated with either "X" or "Y" factors, which may be the cause of symptoms in some patients otherwise evidently treated with maximum doses but who, nevertheless, suffer from some difficulty but not in the same patterned response observed in new and untreated pollinotic patients. This subject will be discussed in a separate communication. The data await corroboration of relationships as has been determined by gel diffusion techniques.

The fourth table lists 130 patients who were treated with amounts of extract ranging in magnitude from 250 to 2000 P.N.U. It must be emphasized, and stated, and re-stated, that these are *not* related to skin test sensitivity, but only to the date the patient reported for his injection. These patients seen at

an earlier date would have been given, and with assurance of absolute safety, 2500, 5000, or 10,000 P.N.U. For the pollen season of 1961 it is anticipated that those who have not been instructed to defer additional injections until symptoms recur, will so be treated. For a few of the patients in whom it is thought that the protection given was not sufficient to permit unlimited exposure to ragweed pollen, there will be administered amounts of emulsified extract of the magnitude of whatever is represented by 15,000 or 20,000 P.N.U., although the relationship of greater quantity to higher levels of immunity has not unequivocally been proven.

TABLE V. TRANSITION PATIENTS
Distribution According to the Number of Months since Injections of Unemulsified Extract had been Administered

Number of months	1	2	3	4	5	6	7	8	9	10	11	12	Transition Patients Total
Number of patients	2	4	4	4	6	4	3	4	1	0	3	3	38

Comment (Table V).—The discerning allergist will be interested in exactly how many patients had previously been subjected to multiple visit types of programs in so far as the protection might have been induced by these and carried over to a second season. The fifth table lists every patient so treated by us or by others. Of the thirty-eight patients, eighteen had ceased treatment by means of such injections from six to twelve months before the receipt of their single annual injection.

It may be said of the others that their injections of unemulsified extract had been administered at intervals of one week. The total number of injections was not great, in that in two patients, fewer than four, and in four other patients, fewer than eight injections had been taken. These injections were looked upon as placebos. In the calculation of the quantity to be given, the fact that injections of unemulsified extract had been taken was not a determining factor. In other words, the effects of previous treatment, if any, were completely ignored. We are faced with a patient who must receive treatment, not for the immediate past, but for the ensuing season. The treatment he has received, when it amounts to a few injections of unemulsified extract, should not be given a second thought. It makes no difference whatsoever in the final results. Those allergists who think that these injections confer any immunity and that a poor emulsion may therefore be injected with greater safety, do not realize to the full that the injections of unemulsified extract in small quantities are, almost all of them, excreted quickly unchanged and are therefore not totally antigenic. Only a small part of the extract does any good, if it does any at all. The emulsified extract is released much more slowly and continuously and acts quite differently. Should the emulsion be poor, the patient who has received several injections of unemulsified extract is not more free of the danger of a systemic reaction. With a properly prepared emulsion it does not matter what injections have

been given and in what quantity or by whom or when. This is easily demonstrated by the administration of an acmic dose of emulsified extract and the almost senseless performance of the skin tests after the event. Allergic allergists may, at first, face an injection so administered with some trepidation; but then, when no reaction has occurred, they invariably see the more amusing aspects of the procedure.

TABLE VI. THE DISTRIBUTION OF PATIENTS ACCORDING TO THE DATES THE INJECTIONS OF EMULSIFIED EXTRACT WERE ADMINISTERED

Month	April	May	June	July	August	September	Total
Number of patients	8	303	745	297	106	42	1501

Comment (Table VI).—From past experience[2] it was known that the ragweed pollen sensitive patients did best when the injections were administered during May and June. Of the 1501 who are the subjects of the present report, approximately two-thirds (1048) were so treated. The patients listed as seen in September could either not keep earlier appointments or were new patients whose symptoms were sufficiently severe as to require what may be termed intra-seasonal treatment. They all presented a history of difficulties which usually extended through mid-October. In other words, any patient who faced the prospect of less than one month of affliction was urged to take treatment for symptoms as represented by bronchodilating or antihistaminic agents or, if need be, corticosteroid hormones, usually methyl prednisolone. These patients, who are not listed, took such medical treatment which might be needed for almost all of the period up to three weeks (or longer when the patient's past and his present did not, for obvious reasons, parallel each other), but they were never completely free of an awareness of their disorder or of the effects of medication.

Those who took injections received a total of either 500 or 1000 P.N.U. in 0.5 ml of the emulsion which was deposited, in all patients, intramuscularly. There were neither local nor systemic reactions. In all of these patients the symptoms ceased within a period of six to twelve days. They thereafter needed no drugs (Table IX).

These patients are apparently too few to warrant a statistically valid conclusion, but they did well, and interestingly enough, so did all of the 106 patients who were clinically well and yet received their injections during August. It is true that a group numbering 148 is no cohort, but one might lean toward the conclusion that August is almost as good a month as is either June or July as regards treatment with the particular emulsion used.

Comment (Table VII).—In all, in only twenty-eight patients could such symptoms as occurred be related to exposure to ragweed pollen. In previous communications insufficient emphasis was responsible for what seems to have been an unfavorable impression of the results of the enapothetic type

of treatment. Some readers, certainly not wittingly, concluded that the quality of the results was only as good as that achieved by traditional methods, excepting for the saving in net hours of injection time, general effort on the part of the patient, and in patients allergic to the one pollen, a diminution in medical costs equal at least to one-third of the previously

TABLE VII. DISTRIBUTION OF PATIENTS WITH SYMPTOMS ACCORDING TO DATE SYMPTOMS FIRST OCCURRED

	August		September		Total
Dates	15-25	26-31	1-18	19-30	
Number of patients	7	10	8	3	28

paid annual fee. Any patient who reported having suffered from any symptoms whatsoever or for any cause as occurring between the first and the last days of the period of pollination was tentatively labeled as a failure of the method of treatment, because other causes of symptoms were sometimes not known or no treatment for them, when practical, had been given. No patient was limited in his outdoor activity. None was told to follow a diet from which foods known to cause symptoms in any particular patient, seasonally or extra-seasonally, were excluded. In other words, the system of treatment was subjected to the most stringent clinical tests that could be conceived. If, despite every obstacle thrown into the patient's path, his clinical course was smooth, then the results achieved by others would be better than ours. And that is exactly as it should be.

At the very worst when every patient who, during the season, suffered from as much as one sneeze (which might have been physiological in origin), or from one wheeze (which, in its turn, might have followed exertion or exposure to cold sea water or cold air, as when faced with an extremely refrigerated environment) was included in the group classified as failures, then at no time was there more than a handful of patients who were not completely free of symptoms.

A patient might volunteer the information that he had been exposed to dog dander which also extra-seasonally always caused nasal stenosis or coryza. It was, in any one set of circumstances, impossible to prove that the particular exposure might only have been followed by the symptoms listed had there been no ambient pollen, or had the patient received a greater amount of extract, or at an earlier or later date. The door was always left open as concerned an improvement in the results obtained because although the patient may be content with his betterment, the physician's standards must not only be higher, but when the clinical disorder permits, be absolute.

It was generally discovered by visiting physicians that patients who had been listed as "failures" as of the antecedent year or years of treatment were not so evaluated by them. It was at the insistence of these physicians that

the facts were presented in their true light. In none of the fifteen or more studies so far published have there been more than two or three failures in every hundred patients treated. But, in every study there have been from 15 to 25 per cent of the patients who, following the first season of treatment, reported that some symptoms had been experienced. There was a total of fifty-two such in the present series. The only method known of avoiding a false conclusion concerning these was to permit independent evaluations of their histories and of their clinical courses, as determined by two separate observers. This procedure established the fact that the reports of difficulty of the other twenty-four patients were not linked to exposure to ragweed pollen.

A lucid example of this, and one which should (but which probably will not) put a stop to all such comments, is the inclusion in the "failure group" of a patient who on the fourth of four days of rain had some hours of symptoms when he used the opportunity to rearrange the furniture stored in his cellar. These symptoms ceased following the use of three tablets of an antihistaminic agent (Actifed,® Burroughs Wellcome & Co.) and did not recur, although the patient thereafter faced the peak of the period of ragweed pollination.

It is of passing interest that many of the patients treated in the distant past by means of programs of multiple injections of so-called progressive increases in quantities of extract administered (although in many instances the extracts lost potency more quickly than the additional quantities given represented) voluntarily reported that following single injections of emulsified extract, they could tolerate the presence of inhalants or the ingestion of foods which have previously resulted in symptoms which were noticeable during the season of pollination. To balance these there were others whose tolerance of such inhalants or foods was greater than it had been but was not absolute. They were, however, content with the results achieved because, in the past, the same type of exposure could be pinpointed as a cause of similar symptoms.

For the present study there were twenty-seven "new patients" who first reported for treatment during late August and early September. Their studies have not been completed. Although well as far as their exposure to ragweed pollen is concerned, the course of their mild, intermittently present symptoms which extended beyond the pollen season (since they are so few) would hardly be worth listing. As these other inhalant and (in one or two) food sensitivities were elicited or discovered, the symptoms ceased. They can certainly not be listed as "failures" as regards the enapothetic type of treatment of ragweed pollinosis.

It may be interesting to note that the numbers listed in the seventh table follow the distribution to be expected. Eighteen of the twenty-eight patients were afflicted between the last two weeks of August and the first fortnight of September, with seven for the fourth week of the season and three for the fifth and sixth weeks, although pollen was ambient until late October.

The pollen season of 1960 differed, however, from any of those studied since 1938. During that year the famous hurricane of September 21 practically ripped all of the leaves off the plants. There was much illness caused by the molds but little from the ragweed pollen, excepting for the two days before the storm, during which the winds from the South brought tremendous quantities of pollens and molds into New England and, as well, distributed the local pollen to the far North and caused symptoms in some of our patients who were then in Alaska.

For the season of 1960, the fifteen days of dry weather which preceded Hurricane Donna were characterized by 0.1 inch of rain. Pollination was not only intense but the plants were observed to have gone to seed before September 12, 1960. The rainfall thereafter for forty-eight hours varied locally from 2 to 3.5 inches. The chenopods and amaranths which often precede or coincide with the ragweed did not go to seed. The excessive rainfall in fields of corn from which the ears had long since been harvested accelerated the growth of secondarily important wind-pollinated plants and it was obvious that, within a radius of 30 miles of Boston, there were tens of thousands of acres of flourishing pigweed. In some areas the individual plants were almost 5 feet high. Although this affected approximately 1 per cent of the patients, it was obvious, by skin and provocative tests, as well as by the pattern of exposure and their geographical areas, that it was at least one of the causes of their afflictions. Although the number is small, these patients, had their particular sensitivities not been known, would have been listed as failing to respond completely to the treatment for their ragweed pollen allergy.

The short and intense ragweed pollen period also otherwise differed from that of previous years. It is customary, in many of the truck farm areas, to gather the produce, and in the case of legumes, as peas, which ripen early, immediately to plow in what is termed the "green manure" so that it may decompose before the planting of the next Spring. The cover crop for stubble mulch is usually any one of a number of grasses but most often either English or Italian rye chosen because either is so hardy.

In the case of a crop of corn, the dry stalks, as chopped by rotary mowers, are taken to within 2 or 3 inches of the surface, and allowed to decompose until after the first killing frosts have freed them of ear worm and corn borer which, if the stalks were to be plowed under, would survive because they would then be below the frost line. When "winter rye" of whatever type is then planted, it rarely grows high and hardly ever reaches the maturity necessary for pollination.

For the Autumn of 1960, as has been noted during occasional years of the past two decades, either because of the dry clear weather after the abundant rain or the high number of solar units present, the cover crops reached maturity at an earlier date, and with the stimulus of the unusual

amounts of rain, more plants attained maturity. In the area of Boston-Plymouth (forty miles), a second wave of grass pollination was obvious to the eye and by examination of the plants. This did not disturb the typical ragweed pollen sensitive patients, but it did cause difficulties in those who were allergic to both grass and ragweed pollens. The symptoms lasted for some days and were noted only by patients in whom the intracutaneous types of tests were, in a sense, qualitative proof of sensitivity present, but the pattern of response and the dates of symptoms were also quite different from those recorded for the patients, new and previously untreated, but allergic to ragweed pollen only. The small number of patients involved would hardly merit the dignity of further analysis or the time and effort needed for tabulation. They are mentioned only because they exist and because any results obtained following any type of treatment, although only symptomatic in nature (if the number of failures is to represent any true evaluation), must take their existence into consideration. No matter how the patients have been treated and by whatever method of administration of extract, they cannot be listed as failing to respond. They were simply not treated with that to which they were allergic. To give them more ragweed pollen extract for a longer period of time will not solve their problem.

The question naturally arises as to why these other pollens are not picked up on the so-called pollen slides. A four-year study convinced us that a 23 x 23 mm bit of vaselined glass placed at three "strategic" places in a city could not possibly reflect what happened to a patient who at ground level drove from one end of it to the other in accordance with any compass points. Patients reported symptoms when the slides were free of pollen and pollens could be collected several hundred meters from a slide on the surface of which none had impinged. On high pollen count days there were few patients who were well and on low pollen count days there were many other patients who, treated adequately by the standards of the time as regarding multiple visit programs, were ill. There were years when the total pollen count was great but the clinical results were excellent. The relationship of low pollen counts and severe clinical symptoms was also noted. The amounts of medicines prescribed proved the "counts" to represent just so much nonsense, because all that the "Spinners" and the air suction types of apparatus tell us is what pollen is in the air at the places where these "games" are played. As far as the literature is concerned, no reports have been made on pollen counts related to reality by known "fall-out" formula, excepting for that of A. Nelson Dingle[3] who quotes Chamberlain's studies and equations for the determination of the velocity of deposition of particulate matter of the magnitude of pollen. The concept is represented by

$$Vg = \frac{\text{Amount deposited by cm}^2 \text{ of surface each second}}{\text{Volumetric concentration per cm}^3 \text{ above surface}}$$

Those who wish to use pollen counts as indications of pollen concentra-

tion, might reflect on the use of the equation for the rate of deposition, w, of particulate matter at the point (x, y), which is as follows:

$$\omega(x, y) = \frac{2Qv_g}{\pi C_y C_z \bar{u} x^{2-n}} \cdot \exp\left[-\frac{4v_g}{n\bar{u}C_z}\sqrt{\frac{x^n}{\pi}}\right] \exp\left[-\frac{y^2}{C_y^2 x^{2-n}}\right]$$

The penetration rate of pollen with a building of standard construction depends on the direction of the wind and on its velocity. It is not represented by "a simple curve" and theoretically leads to the differential equation

$$\frac{dx}{dt} = k\,(m - x) - \frac{wx}{h}$$

in which k represents the ventilation rate and x the pollen concentrations in the space in that of the outdoor air, w, the speed of fall of the grains of pollen in undisturbed air, and h, the vertical height of the area—in which case, dx/dt expresses the rate of change of the pollen concentration.

Given such theoretic considerations it is obvious from the practical point of view of any one patient, that the pollen count obtained from a slide placed on a seventh floor ledge of a city office building is not related to the pollen concentration of the patient's bedroom of a house situated in the country and exposed to a 10-mile wind sweeping over a vacant lot invaded by a solid growth of ragweed plants located windward and perhaps only 50 meters distant.

It is for these and other reasons that Dingle *(op cit)* says, "Thus the meaning of a pollen sample changes drastically with the conditions of air movement under which it is collected, and it is very difficult to establish a good model that would represent the spacial distribution of pollen grains in the air at any instant. Because of these factors, it must be recognized that an isolated pollen count has complete validity only for the place and time of its collection. It does not necessarily characterize the pollen exposure of any particular hay fever patient, and by long odds it probably differs greatly from his exposure. This should serve in part to explain the disparity between the traditional 'pollen counts' and the clinical symptoms displayed by individual patients."

"Inasmuch as the traditional 'pollen count' is a twenty-four-hour sample accumulated upon a 'gravity slide,' one should understand that it has no validity whatever as a representation of the number of pollen grains per unit volume of air. Further, because it is usually collected at a local hospital or U. S. Weather Bureau observing station, it cannot, except in the most tenuous way, characterize the general level of air pollution by pollen grains. Clearly, if there is to be an official published pollen count for a city,

it ought more properly to be an average of numerous volumetric samples taken so as to characterize the bulk of human environments in a city."

He uses an illustration of a study by Löbner (done in 1935) of dust distribution at a street crossing in Leipzig and asks, "At which point should one sample to determine a representative 'pollen count'?"

TABLE VIII. APPARENT RELATION OF SYMPTOMS TO DOSE LEVEL

Dose in P.N.U.	500	1000	1500	2000	2500	3000	4000	5000	6000	7500	10,000	Total
Number of patients	1	0	1	0	19	0	0	5	0	0	2	28

Comment (Table VIII).—As noted, there is, in this study, no concordance between the skin test reactivity and the amount administered if only because the skin test response was given no consideration whatsoever. But of interest is the fact that, of the twenty-eight patients, twenty-one received the smaller numbers of units. It had falsely been concluded from the few patients represented by the previous study published that there was perhaps some relationship between the dose and the effects, because in this study of 1064 patients[4] almost twice as many, namely ninety-seven of 144 treated with 4000 P.N.U. or fewer had developed symptoms as compared to forty-seven of the 144 who had received injections of 5000 P.N.U. or more. But, although the number of the first was twice as great as the number of the second, the two numbers represented little more than one Standard Deviation, more or less. The trend toward more frequent symptoms, when the amounts given were smaller, could be discerned.

When the notion of basing the amount upon the fortuitously-present skin test response, regardless of its size, was abandoned, the better results obtained by the administration of the larger amounts of extract progressed from a trend to a conclusion long since forgone, and in accordance with the actual experiences of the senior allergists in practice thirty or more years.

A comparative study of the fourth and eighth tables brings to light the fact that nineteen of 421 patients who received injections of 2500 P.N.U. suffered from some symptoms, but only two of 480 who received 10,000 P.N.U. Intermediate between these numbers, there are five of 424 who were treated with 5000 P.N.U. The progression of nineteen, five and two is statistically valid and speaks for itself, because by no manipulations can the significances be changed. The other two patients received injections, the one 500 and the other 1500 P.N.U.

All of the usual and (in many cases) superficial objections to these conclusions can quickly be dismissed. These few patients with symptoms were not either more or less sensitive, or early or late, or allergic to other substances. They were not patients in transition from other methods of traditional treatment. Some had done well on the same dose and, for no good reason, it was again administered. Others went out of their way and faced heavier exposure during a short but intensely heavy period of pollination.

Some of the arguments previously advanced for the basis of the dose on the skin test response may appear convincing, and some of the conjectures may actually represent some truth. None matter. The fact is that twenty-six of twenty-eight patients who, it was thought, would be well did not respond with perfect tolerance to whatever immunologic change may be characteristic of allergic patients treated by injections of pollen extract in whatever form. It would appear that the amount received was low and that this is the most important or more obvious variable. Had we possessed the foresight, these patients would have been treated with larger quantities of extract. It may also be true that these patients were allergic in part to another seasonal allergen. All such "failure patients" are at present undergoing study and will be the subject of a separate report. The one factor of the ratio of dose versus results can then most easily be contesserated.

TABLE IX. APPARENT RELATION OF SYMPTOMS TO DATE OF ADMINISTRATION OF INJECTION

	April		May		June		July		August		September		Total
Dates	1-15	16-30	1-15	16-31	1-15	16-30	1-15	16-31	1-15	16-31	1-15		
Number treated	8		303		745		297		106		42		1501
Number with symptoms	0	0	1	7	8	5	5	2	0	0	0	0	28

Comment (Table IX).—The ninth table clearly demonstrates that the patients who reported for treatment of their symptoms had received their injections between the dates represented by the last two weeks in May (all but one) and the first fortnight of July (all but two).

TABLE X. DOSES RECEIVED BY PATIENTS WHO SUFFERED SYSTEMIC (BY DEFINITION) REACTIONS

Dose (in P.N.U.)	1000	1500	2000	2500	3000	5000	6000	10,000	Total
Number of patients	0	0	0	10	0	2	0	0	12

All of the twelve patients listed in the tenth table received a type of emulsion no longer in use. The urticarial reactions were not related to skin test reactions or to quantity administered.

Comment (Table X).—As knowledge of emulsion chemistry increased, the properties of the emulsions of pollen extract prepared were such that fewer and fewer reactions, and those more and more fleeting, were seen. After the patient, who in a series of 1501, is represented by the consecutive number 790, had been treated, no more reactions were seen. In the 790 patients, eleven other mild urticarial responses had been reported, but in some of these the injection cannot, of itself, be incriminated. When a patient reports for treatment of pollinosis and urticaria and takes no antihistaminic agent

so that a qualitative test for the pollen in question may be performed, certainly the hives present daily before and after the injection cannot satisfactorily be proven as due to the injection. The systemically reactive patients, especially those who respond to injections of saline with urticaria, possess in common many characteristics of interest. Before they become a subject, only of historical interest, they deserve a study devoted to them alone. This will appear in due course. No reactions have since occurred in an unbroken series of 13,511 injections. Because of the use of the previously noted two oils, two emulsifying agents and the stabilizing substance, none are expected, excepting as a result of a patient's ingestion of allergenic foods, large amounts of alcohol or technical error. Every possible step has been taken to assure that the latter does not occur, and it is no longer, in any case, a matter of great importance.

The studies and demonstrations have shown that for practical purposes the factors of safety are so great (especially in a new patient), that any amount of emulsified extract is safer than any amount of unemulsified extract. Systemically reacting patients titrated to the smallest amount which had resulted in an induced reaction have, weeks later (so that recalcitrance could not possibly be the result of the reaction), taken up to 25,000,000 multiples of the same quantity with no local swelling or systemic effects. The physician at first is fearful of the amount the injection of emulsified extract represents because he thinks of the total quantity and not in the different frame of reference concerned with rate of absorption. As he notes the absence of reactions and the better results following enapothetic treatment, his attitude changes so that he begins to fear to inject any quantity, however little, of unemulsified extract. This experience has been that of several hundred physicians and is the everyday routine attitude of the allergist well trained in the preparation and administration of emulsified extracts and vaccines.

DISCUSSION

There is so little to discuss. Not one objection to the enapothetic type of treatment has stood the simple test of time. Any one may be valid when it is concerned with emulsions made by hand and not subjected to more rigid control techniques. The same test of time has shown that with poor emulsions, some reactions will occur. The results will be no better than with emulsified extracts except for the saving of time. The use of placebos in the same hand-made emulsion in transition patients represents a complete waste of time and effort. The satisfactory results following such so-called placebo injections must, of necessity, be high. No one knows how many patients previously treated with large doses of unemulsified extract will experience a satisfactory season if it were possible that the two seasons and the amount of exposure could be equated. The adjuvant effect of the mineral oil alone in previously treated patients is, although known to occur, not measurable in such experimental studies. There is no such entity as a true placebo, but in

any case the use of another oil injected in previously untreated patients would more closely approximate the non-existent ideal. No other type of study can, on deep reflection, be considered, in every sense, scientific in method. It proves nothing. It does not add to the sum of useful knowledge. But it is, after all, the patients who are content with the results, which are in every sense of the word better, when a sufficient amount of extract has been administered.

Experience with patients chosen chiefly because of their manifest hypersensitivity has led us to prepare more complete emulsions. Safety no longer is a matter of concern. The results have been better. They are not yet good enough! Our standards must be such that the patient must know that when he takes an injection of emulsified pollen extract, he must of his own volition truly go far out of his way to discover whether the pollen to which he is allergic is at the moment in the air. All other arguments are meaningless because the only true test of the efficacy of any type of treatment is the patient's response to exposure. When he can walk into a field and unknowingly stay in it for hours with ragweed pollen visible on the tip of his nose and yet show no signs or symptoms of pollinosis, he can tentatively be said to be doing rather well. The purpose of the study would then appear to have been justified.

SUMMARY

A population of 1501 patients, who resided in almost all of the ragweed pollen areas of the United States and Canada, and who were clinically allergic to the pollen itself, received enapothetic injections of emulsified ragweed pollen extract. These were administered with complete disregard of skin test or other supposed laboratory or office methods of measuring or judging degrees of sensitivity. Twenty-eight patients reported symptoms. Of these, twenty-one received injections of 2500 P.N.U. or fewer; five patients, 5000; and two others 10,000 P.N.U. Twenty-four other patients experienced some symptoms which in each were not related to exposure to the ragweed pollen.

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Progress in Allergy

HUMAN ECOLOGY AND SUSCEPTIBILITY TO THE HUMAN ENVIRONMENT

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(Continued from May issue)

Part III. Air Pollution

Whether a person is aware of the impingement of chemical air pollution on his health and behavior depends principally on: (1) his degree of susceptibility and (2) frequency of exposure to such agents. Since this presentation is principally concerned with the highly susceptible patient, the intermittency or constancy of exposure becomes the most important variable in the ability of both patients and physicians to recognize the causative roles of environmental chemicals.

Many other writers[19-26] either described or reported the clinical effects of intermittent air-borne chemical exposures, but the concept that a given person might be susceptible to many materials of *common chemical genesis* was slow to be appreciated. Vaughan[27] was impressed with the relationship between artificialities of the environment and diet of man and allergy. Coca[24] and Brown and Colombo[19] listed odors of utility gas, kerosene, and other solvents including evaporating paint, motor exhausts, wood and coal smoke, and newsprint odors as excitants of clinical reactions.

Acute immediate reactions occurring in previously symptom-free, out-of-town patients upon entering Chicago usually are readily detected. Indeed, a study of the problem of urban air pollution was prompted by the observation that certain patients living to the east and northeast of Chicago invariably became sick during and after passing through an area containing refineries, steel mills, chemical and paint manufacturing plants. Some noticed only mucous membrane irritation. Others became nervous, jittery, irritable, and hyperactive initially with delayed rhinitis, bronchitis, asthma, fatigue, headache, or painful musculoskeletal syndromes. In a few extreme cases, the patient became pseudo-intoxicated initially before lapsing into stuporous depressions. Because of the acuity of these reactions in previously unexposed persons, some drove an additional 50 miles in order to avoid this area when entering Chicago. Fortunately, with new roads decreasing exposure time and the use of *activated carbon filters*, the most susceptible patient may now drive through this region without reaction.

Once the immediate and delayed phases of this clinical picture attribut-

able to intermittent air-borne chemical exposure had been recognized, Chicago residents manifesting similar but more chronic symptoms were studied. Gradually, over the past decade the apparent full range of impinging chemical exposures as well as their clinical effects became evident.

It should be emphasized that the geography and weather of this region favor an intermittency of atmospheric pollution and facilitate the investigation of this problem. (1) East winds from Lake Michigan frequently interrupt other winds, thus intermittently clearing the blanket of polluted air overhanging the city. (2) The correlation of clinical symptoms with wind direction is facilitated here by the location of the major industrial installations on one side of the city. (3) The uncommon occurrence of the meteorologic phenomenon of inversion, the common presence of relatively non-polluted turbulent winds from any quarter, and the absence of natural obstructions to winds also favor intermittency of exposure and acute reactions. Although these factors tend to decrease the extent and chronicity of illness (due to susceptibility to chemical exposures), and to aid its detection, Chicago still has a *major outdoor air pollution problem.* But, when this knowledge was applied to instances of chronic illness in patients known to be susceptible to diverse chemical exposures, it soon became apparent that outdoor chemical air pollution accounted for *only a portion* of the morbidity of chemically susceptible individuals.

Other readily apparent portions of the chemical environment impinging on susceptible persons consisted of certain *intermittently used* synthetic chemical drugs, cosmetics, and such variable personal contacts as exposure to the odors of fresh paint and solvents, insecticides, perfumes, et cetera. In fact, the total effects of such readily detectible intermittent exposures might be likened to the visible part of an iceberg.

It was not until patients suspected of having the chemical problem were studied by means of *comprehensive environmental control*[3,4] that the writer became aware of the causative roles of related, but less often suspected, chemical exposures. These might be likened to the *submerged* portion of an iceberg. As a result of this experience, the preponderant significance of *indoor chemical air pollution* became apparent. At least in the Chicago area—and similar conditions apparently exist elsewhere—*indoor* chemical air pollution is a more important cause of chronic debilitating illness than chemical pollution of the *outdoor* atmosphere. Indeed, it is the most subtle to recognize and, singly, the most important phase of the total chemical problem. It must be brought under control before the clinical effects of other facets of the chemical environment may be correctly appraised.

Other hidden portions of the problem comprise such exposures as *chemical additives* and *contaminants* of the *diet, water supplies* and *biologic drugs* as well as maintenance dosage of synthetic drugs or daily contact with synthetic textiles and certain other personal contacts. Whereas the clinical effects of indoor chemical air pollution are most troublesome in winter months and are usually confused with the effects of exposure to house dust,

it is the "maintenance" doses of chemicals in food, water, drugs, cosmetics, and some personal contacts which, in their totality, constitute never-ending and usually unsuspected sources of exposure.

When the clinical effects of these usually hidden facets of the chemical environment were demonstrated in susceptible persons, the proportion of their illness attributable to previously suspected, more readily apparent chemical exposures changed markedly. Such a change is often indicated by having the diagnosed and controlled patient *re-check* his original questionnaire in *red pencil.* In other words, the full range and clinical significance of the pathogenic chemical exposures for a given individual are not appreciated until *after* avoidance of the chemical environment in its totality and re-exposure to its constituent parts. Although the chemical problem must be recognized and treated in respect to all of its facets—and each patient presents a highly individualized constellation of susceptibilities to such facets—it is necessary to present the subject in sections.

A. INDOOR CHEMICAL AIR CONTAMINATION

Since a knowledge of indoor chemical air pollution is a *must* before attempting to interpret the clinical effects of other chemical exposures, the major sources of air pollution in homes and public places will be described and their relative importance discussed.

Should the reader be concerned with the scope of the chemical environment and the negative incriminatory approach in the body of this article, a positive approach in the form which may be used for instruction of patients will be outlined as a summary.

Fuels, Solvents, and their Combustion Products

Fuels.—Storage of hydrocarbon fuels in the basements of homes is a potential hazard for chemically susceptible patients. Kerosene, used to wet down coal to control dust in delivery, slowly volatilizes and contaminates the air of the basement. There is also a troublesome odor arising from oil storage tanks located in the basement, as well as the additional hazard that they may be overflowed in filling. Once a basement floor has been flooded with fuel-oil, this odor tends to remain for several months or even years, and may necessitate abandonment of such a home. Also, most fuel-oil installations—whether furnaces or space heaters—impart a characteristic odor. Although more odorous when operating, there may be a sufficient odor when not operating to cause symptoms in a highly susceptible person.

Despite the fact that utility gas is the cleanest of the readily available fuels, it is also the most hazardous for the majority of chemically susceptible patients. It seems to make little difference whether artificial or natural gas is used, although the relatively high pressures under which natural gas is currently delivered may increase this hazard, especially if home installations have been designed for *lower* pressures. As a consequence, every joint and turn in a utility gas line is a potential and ofttimes an actual point of

slight leakage. Utility gas, being lighter than air, tends to rise from the basement or kitchen through the remainder of the house. The greater the amount of piping and number of outlets, the more pilots and other automatic devices on gas utilities, the greater the potentiality and probability of leakage.

Chronic symptoms may be maintained in the highly susceptible patient living in a gas utility home. This is due to *leakage of unburned gas,* even though all pilots are turned off, no gas is burned, and despite the report of the utility company that gas leaks cannot be detected. Devices for detecting gas leaks are relatively unsatisfactory and are no match for the extreme susceptibility of certain individuals. *Acute reactions* have been induced in such persons when returning to such a home after a period of absence during which the patient in question had not been exposed to utility gas and related chemical exposures, and when relatively symptom-free at the time of such a re-exposure.

Combustion Products of Fuels.—Coal-burning stoker furnaces sometimes burn back into the coil-stoking mechanism and contaminate basement air. Coal burning in open fireplaces is apt to puff at times, discharging a greater quantity of gas and smoke than may be drawn off by the chimney. A downdraft through an unused fireplace from a double chimney containing both fireplace and furnace flues, may carry combustion products from the furnace or incinerator which may foul living quarters and cause serious unsuspected reactions. This may be obviated by keeping a fire in the fireplace when an adjacent flue is being used under atmospheric conditions favoring such downdrafts.

The fuel-oil-burning space heater and kitchen range are *major causes* of indoor air pollution and respiratory symptoms, as reported by Brown.[20] In the writer's experience[7,18] they are also common causes of other symptoms, especially depressions and musculoskeletal painful syndromes. Fortunately, these installations are less common than formerly.

Indoor air pollution arising from the combustion of furnace fuels seems to depend more on the type and location of the *furnace* than the type of *fuel* used. Warm air furnaces are more troublesome than other types, even though they may be in good mechanical repair. This statement is based on the *clinical experience* of the change-over from warm air furnaces to hot water or steam systems in homes of over fifty patients and supervising the moving of approximately 100 families from warm-air-heated homes to those heated electrically or by means of hot water or steam systems.

Warm air systems may pollute the air of basements by the emission of combustion products through draft apertures as a result of "puffing" each time the gas-fired furnace turns on. Major leaks between the combustion and warm air chambers of the furnace are not uncommon. It is also known that warm air furnaces result in more turbulance and dust disposal than occurs with the use of certain other types of heating equipment. But the

speed with which some chemically susceptible persons react to being in the draft of a warm air register as the furnace in good mechanical repair turns on, suggests some additional mechanism. Since these observations have been made with dust-sensitive patients and are more pronounced in cold weather, there is a possibility that an additional toxic factor may be imparted to dust-laden air as it passes over an extremely hot furnace dome. In a few instances, these apparent reactions to "fried dust" have been lessened by the installation of electrostatic filters in the duct system of the furnace. This subject is in urgent need of more detailed investigation.

Air contamination of the home, resulting either from fuels or their combustion products, is relatively increased in basement apartments or in living quarters directly *over* furnace rooms. Indeed, the location of the furnace, irrespective of its type or the fuel used, is of utmost importance. The worst location is in the center of the main floor of a ranch-type home or in an open utility room on the same floor as the living quarters. The ideal location for a furnace—and the only one recommended—is *outside* of the living quarters. This means either in the garage, in a separate room between the house and the garage, or in a completely exteriorized room adjacent to the house which is entered only from the outside. When so located and without direct communication with the house (except for the entrance of the hot water or steam pipes) there seems to be little choice between the use of coal, oil, or gas fuels as long as warm water or steam central heating is employed. Although electric heating is preferable, any type of room-heating unit containing motor-driven fans is not desirable, since the heat of the unit apparently volatilizes the oil of the fan motor, and this, apparently, induces symptoms in certain highly susceptible persons.

Preliminary evidence suggests that the relatively "cool" heat provided by heat pump electrical installations is preferable to the presence of extraordinarily hot electrical resistance coils. In this connection, two-stage controls of baseboard electrical heating systems are preferable to one-stage controls, since with the former the temperature of the home is maintained most of the time by means of less hot electrical resistance units.[28]

Second to such relatively low temperature electrical heating installations, hot water systems are slightly preferable to steam heat, since the volatility of chlorinated-fluoridated water may be responsible for inducing chronic symptoms in certain persons.

Although the installation of mechanical and electrostatic filters in warm air heating systems is helpful in removing dust and other particles, they do *not* remove odors and fumes. In the homes in which this has been tried, installing activated carbon filters in hot air systems in conjunction with the use of electrostatic filters has been less satisfactory than changing to a relatively "cool" type of electric heating or to hot water systems in which the source of combustion is *outside* the living quarters.

The gas-fired kitchen stove's contribution to air contamination of the modern American home is so preponderant that it must first be removed

from the premises before other local sources of indoor air pollution can be evaluated. This statement is based on the writer's experience in causing to be permanently removed over 500 such kitchen ranges from the homes of patients susceptible to chemical odors and fumes. One of the most amazing results of this experience is that the writer has *not* received a major complaint from this group of patients regarding the expense of such a move. Once the indications for the move are present and the patient complies with the advice, resulting *clinical improvement* apparently has justified the expenditure.

Air contamination arising from the gas kitchen range *cannot be adequately eliminated* by such part-way measures as increasing ventilation in the kitchen, keeping the kitchen door closed, installing a kitchen exhaust fan, turning off the stove's pilots, disconnecting the stove but leaving it in the room, or even by turning off the gas at the point where the gas line enters the house. Although any or all of these measures may be helpful, their relative ineffectiveness should be stressed in view of the *seepage of gas odors* from disconnected utilities and piping which may persist for many months. The most satisfactory way to evaluate the clinical effects of the gas range on the health of a chronically sick person is either to remove the stove or the patient, temporarily, and then note the effects of re-exposure. If the patient is removed, it is essential that he remain *chemically unexposed* while away; that such kitchen contaminants as bleaches, ammonia, plastics, detergents, et cetera, be removed from the room, and upon returning, that the patient remain for two hours in the kitchen before entering other parts of the house. Even then, symptoms may not be evident until during or following the first baking day when there is a heavy gas exposure.

The gas refrigerator, especially if installed in a small tight kitchen, is also a major cause of indoor chemical air pollution. If there is a double installation, both the gas stove and the gas refrigerator should be removed concurrently and replaced singly. The same procedure should be applied to gas driers.

Perhaps the most pernicious single gas-burning device is the unvented gas-burning room wall heater, used so frequently in the Southwest. In the writer's experience, this installation is one of the chief reasons for the *perpetuation* of chronic symptoms, especially asthma, arthritis, and mental syndromes, in persons migrating to that area for their health. Although unvented devices in the middle of the room are worse than vented wall units, neither is to be condoned—either therapeutically or prophylactically.

Fresh Paint and Varnish.—Evaporating paint, varnish, and other solvent exposures have long been recognized as precipitating factors in bronchial asthma and other allergic-type responses, including more generalized effects. Fortunately, most susceptible persons are aware of the ability of such exposures to induce reactions because of their intermittent dosages. There seems to be little difference between the effects of turpentine and mineral spirits except that some individuals may be more susceptible to one. Indoor

painting is best done in summer months, but irrespective of the time of year, victims of this illness should evacuate the premises during and for several days following any type of painting or varnishing in the home.

Casein and alkyd based paints are the most satisfactory substitutes, but the highly susceptible person cannot expect a nil effect from the use of so-called non-odorous paints in closed quarters. Rubber based paints are *not* to be used. Although the odor at the time of application may not be extreme, the persistence of this odor for many months may be responsible for perpetuating chronic effects.

Cements and Other Adhesives.—Other major exposures include evaporating solvent constituents of finger nail polish, finger nail polish remover, shoe polishes, paint removers, hinge looseners, adhesives used in model airplanes and other toy fabrications and repairs and also those employed in laying tile or flooring. Some adhesives used in laying tiled surfaces may require several weeks to evaporate fully. Adhesives containing tars used in laying floors are especially troublesome—a hazard that is increased in the presence of heating units in the floor or in the ceilings of downstairs rooms.

Cleaning Fluids and Lighter Fluids.—Highly susceptible persons may react to volatile hydrocarbon residues from the mere presence of or from wearing or pressing recently cleaned clothing. In such an event, the work of various cleaners should be compared, inasmuch as the cleaning fluids used by some are apparently of higher grade than others. On-the-floor cleaning of rugs or indoor cleaning of furniture with solvents should be done during a susceptible person's absence and thoroughly evaporated before his return. Home cleaning with solvents should be attempted *outdoors only,* with due regard to wind direction. The materials should be dry and well aired before they are brought into the house. All cleaning and lighter fluids should be stored *outside* the living quarters. Since combustion products used in cigarette and other lighters may precipitate acute attacks in susceptible persons, their presence or use should be barred.

Newsprint.—The odor of fresh newsprint constitutes a troublesome exposure for many persons. The mere presence of fresh newspapers in the house may not be tolerated by some, but the most troublesome exposure comes when the newspaper is first opened. Consequently, having someone else first read the paper or placing it in a warm oven for a few minutes, then allowing it to cool before reading may help.

Alcohol.—Inhalation of the odor of rubbing alcohol frequently induces acute reactions in the home as well as in physicians' offices. Fumes of alcohol are also encountered in evaporating shellac, brush cleaning preparations, and alcohol heaters and lamps. Synthetic alcohol is commonly employed in the

manufacture of flavoring extracts and may cause inhalation reactions as it evaporates.

Refrigerants and Spray Containers

The slow escape of refrigerant gases from electric refrigerators and air conditioning equipment may cause chronic symptoms in highly susceptible persons. This is sometimes suggested by a gradually decreasing frosted surface or by reactions to stored or frozen foods when the same lot of food, prior to freezing or storage, had not reacted.

The same compressed gas is the most commonly used propellant in spray containers employed in dispensing insecticides, perfumes, hair sprays, drugs, and foods. Since many of these *materials* sold in this type of container are capable of inducing susceptibility reactions in their own right, these reactions must be differentiated from those attributable to the *propellant* of such devices.

Insecticides

DDT and related chlorinated hydrocarbons, being relatively insoluble in water, are usually dispensed in kerosene or other solvents. Whether the deleterious effects of such mixtures in chemically susceptible persons are due to the *active principles* or the *vehicles* is often difficult to determine. The exceedingly high degree of susceptibility of many persons to such mixtures containing lindane, methoxychlor, DDT, chlordane, malathione, or thiocyanates precludes their use as aerosols indoors.[29] Rugs are often moth-proofed by the use of DDT in rug shampoos or storage. Although such residues may be largely removed in cleaning, it should be remembered that some cleaning fluids also contain DDT and that rugs and blankets are usually moth-proofed when cleaned, unless otherwise requested.

Toxic insecticides, such as dieldrin, chlordane, or pentachlorphenol are often used by professional exterminators for the control of termites and ants. These chemicals should not be used indoors—that is, in the basements or attics of homes of patients known to be susceptible to other chemical exposures. Once these materials are applied, it is impossible to remove them. The only alternative in certain extreme instances has been for susceptible persons to abandon such homes in order to control their chronic symptoms. The odors of slowly evaporating moth balls, cakes and crystals containing naphthalene, paradichlorobenzene, and similar materials are also major causes of symptoms in these patients.

Sponge Rubber

Little attention has been paid to the fact that odors arising from sponge rubber pillows, rubber mattresses, rubber upholstery, rubber rug pads, rubber seat cushions, rubber typewriter pads, rubber floor pads, rubber backing of rugs and certain other noise-reducing or shock-absorbing installations in the home are major causes of chronic symptoms. Many patients, having sub-

stituted sponge rubber for other bedding and upholstery in order to avoid exposure to house dust, find to their dismay that the *rubber odors* are more troublesome. Patients rarely are able to detect this themselves since this cause of chronic symptoms has not been publicized, and victims are rarely ever free of such exposures for more than a few hours at a time.

Nevertheless, a highly susceptible person may experience flushing of his face, irritability, and a sense of "stuffiness" or absence of available air upon first entering rooms with rubber rug pads, upholstery, or rubber tiled floors. Nocturnal syndrome characterized by restlessness, insomnia, night sweats and/or residual myalgia and fatigue often suggests the presence of susceptibility to rubber pillows, mattresses, or the rubber insulation of electric blankets.

The demonstration of sponge rubber as a major source of indoor chemical air pollution and susceptibility to it is best accomplished after the elimination of gas kitchen utilities. A satisfactory way to determine this is to place *all* sponge rubber items in a single tightly closed room for a week. Provided other exposures bearing on this problem are controlled, chronic symptoms of a susceptible person are apt to *improve* during this period of avoidance and are also apt to be induced *acutely* soon after breathing the air of this room.

Plastics

The more flexible and odorous a plastic, the more frequently it contributes to indoor chemical air pollution. Bakelite and cellulose acetate products, vinyl floors and surfaces and formica table and counter tops are rarely incriminated, except for an occasional reaction to vinyl and formica as a result of direct skin contact, especially in warm weather. Vinyl and other hard plastic flooring used *in association with* radiant floor heating have been incriminated as causes of chronic symptoms in winter months, but this is believed to be due largely to susceptibility to the *adhesives* rather than to the flooring. Detection is also difficult to unravel if such floors have been *waxed*.

Plastic pillow and mattress cases, upholstery materials, folding doors, shoe bags, hand bags, and other cases seem to be the most troublesome offenders. Plastic brushes, combs, powder cases, shoes, and other articles of clothing may also be incriminated occasionally.

If rubber and plastics both are proscribed, one might inquire how the house-dust exposure problems are handled. In the writer's experience, the majority of house-dust-sensitive patients are able to sleep on feather pillows if these are laundered several times a year. Dacron pillows are not satisfactory substitutes. The dust problem associated wih mattresses, upholstered furniture, rugs and rug pads is handled by frequent cleaning in the patient's absence. Injection therapy with extracts of house dust may be necessary.

Mechanical Devices

Evaporating oil from mechanical devices in the home may also be causes of chronic or acute symptoms in highly susceptible persons. The most commonly encountered illustration is the person reacting to air conditioning equipment, traceable to oil-impregnated glass-wool or fiber filters. In several such instances, the same equipment using *unoiled* filters has been used without reaction. Such persons are usually suspected, erroneously, of being susceptible to chilling or to house dust, but a carefully taken history generally indicates certain air conditioning installations which are *not* troublesome. As previously mentioned, electric or hot water room heating units incorporating a *fan* and *motor* have been found to be relatively common causes of reactions.

Selected instances have been found in which several electrical mechanical devices in small indoor kitchens perpetuated chronic symptoms. For instance, the presence of an electric refrigerator, deep freeze, and water cooler in a small room may contribute materially to the air contamination—sufficient to cause symptoms in occasional patients. This problem has been handled by placing these installations in an adjacent room which is entered only occasionally, or by facing such mechanical devices into the kitchen, leaving their backs—and their motors—in an adjacent room.

Automobiles

Since the automobile is becoming increasingly a part of the home—both in respect to the incorporation of the garage in the structure of the house and from the amount of time some persons spend in their cars—it should also be considered.

Garages should *not* be incorporated into the basements of homes or apartment buildings unless elaborate precautions are taken to prevent the garage odors from rising and fouling the air of living quarters. Whether this can be accomplished is extremely doubtful. Even a direct passageway between the house and an adjacent garage or a common attic may permit the entrance of sufficient car fumes to cause reactions in highly susceptible persons. Careless construction, in which cold air intakes are placed too close to garages or areas fouled by garage odors or other exhausts, often comes to light during routine inspection of homes of highly susceptible persons having unexplained chronic systems.

The air of apartment buildings is often contaminated by garage odors from lower floors. This may occur as a result of frequent passage between the garage and the lobby, owing to carelessness in construction, or failure to close doors between these two portions of the building. Garage odors often enter elevator shafts from conveniently placed basement openings and foul the halls of upper floors.

Miscellaneous

Inhalation of the odors and fumes of detergents, naphtha-containing

soaps, ammonia, Chlorox, cleansing powders containing bleaches, window washing compounds, certain silver and brass polishing materials, and burning wax candles may cause chronic or acute symptoms. The mere storage in the home of bleach-containing cleansers has been incriminated. In general, this group of patients have far more tolerance for unscented soaps and cleansers and for abrasives without added bleach.

Highly scented soaps, toilet deodorants, and disinfectants—especially pine-scented, phenol-containing, or those with pungent chemical odors—are common causes of indoor air pollution to which many individuals are highly susceptible. So-called "air improvers" which depend upon the evaporation of chemical ingredients are also common causes of reaction. The incorporation of phenol and chemicals employed for extermination in the paste of wall paper recently has come to light.

Pine exposures, either from Christmas decorations or from burning pine wood in fireplaces, trouble some patients.

Although creosote rarely enters the home except occasionally in medicinals, one susceptible patient was forced to sell his home because of the odors of creosote arising from the close proximity of radiant heating floor units and creosote-impregnated floor supports.

The storage of highly scented perfumes and other cosmetics may be sufficient to foul the air of homes.

Odors arising from prolonged use of television and radio sets may foul the air in the vicinity of such devices.

Public Places

Indoor chemical exposures found in public places are much the same as in homes except that the use of deodorants, disinfectants, pine-scented sweeping compounds, and sprays for insect control may be encountered even more commonly. Most troublesome of these are the pine-scented or chemical deodorants of public toilets. Acute reactions of patients following such exposures are becoming increasingly common.

Fuel-oil or gas space heaters are also found more often in small shops, stores, and restaurants than in homes; these are major causes of *chronic* reactions in workers and *acute* responses in customers. Although the heating facilities of larger buildings, such as schools, factories and office buildings are generally more satisfactory, there are many exceptions to this statement.

Improper school room heating is a major reason for the poor performance of susceptible children and/or their teachers. This frequently gives rise to the hyperactive, inattentive, irritable, tired, and day-dreamy child. Even more acute reactions may manifest as *extreme* hyperactivity, flushing of the face, unteachability, and the compulsive desires to run and race aimlessly. A sleepy mathematics teacher in a room directly above the school cafeteria, from which gas stove odors arose through an open stairwell, improved greatly in his health and performance when transferred to a more

distant room. *Indoor chemical air pollution of schools* as a contributing cause of poor scholastic performance of susceptible children and the dopiness and confusion of susceptible teachers *is rarely diagnosed correctly!* Other susceptible teachers among the writer's patients have been helped by being transferred from classrooms directly over the furnace room or in close proximity to the indoor swimming pool and shops, thus being spared the odors arising therefrom. The problem presented by indoor air pollution is sufficiently acute to warrant the transfer of certain highly susceptible students and teachers to more satisfactorily located, constructed, equipped, heated, and ventilated schools. Exposure to tobacco smoke in college classrooms also is a major problem.

Chemical indoor air pollution in offices differs from that in homes. There are exposures to carbon paper, inks, mimeographing and duplicating devices, rubber cement, typewriters, typewriter pads, perfumes worn by women employees; also certain occupational hazards at times as a result of the office being adjacent to or sharing common heating and ventilating equipment with shops and warehouses. Many individuals susceptible to chemical exposures are also highly susceptible to tobacco smoke—an exposure that often reaches heavy concentrations in many offices.

Chemical air contamination of hospitals is contributed to by the gas utilities of laboratories and kitchens; chemical deodorants, disinfectants and cleansers; the odors of ether and other volatile anesthetics blown off by recently operated patients; odors arising from the use of certain drugs; the odors from rubbing alcohol; perfumes worn by hospital personnel and visitors; rubber draw sheets and other rubber and plastic bedding and furniture.

Chemical air pollution of churches centers about the gas utilities in the kitchens, the burning of wax candles and incense, perfumes and the odors of recently stored furs and outer clothing.

Hotel exposures are essentially the same as those in homes and apartment buildings. The most troublesome air contaminants are the pine and chemically scented toilet deodorants, sponge rubber and plastic bedding and furniture.

The air of supermarkets and other retail grocery stores is frequently fouled by the odors of insecticide sprays, disinfectants, deodorants, and pine or chemically scented cleaning compounds. The practice of spraying disinfectants over and around fruit and vegetable counters is deplored, both on the basis of contamination of air and of produce.

Indoor chemical air pollution of schools, churches, hospitals and other public places reflects the extent of *outdoor* chemical air contamination of the general area as well as pollutants arising from adjacent parking lots. This may be from the volatility of the cars or from the extensive asphalt surfaces of such areas.

Although *occupational* exposures are beyond the scope of this presentation, the most troublesome fumes and odors for the group of patients under

consideration are evaporating solvents and their combustion products; the odors of rubber, plastic, resins, detergents, cutting and lubricating oils, sulfur, chlorine and other halogens. The interested reader is referred to reviews bearing on the question of individual susceptibility to occupational exposures.[30,31]

B. OUTDOOR CHEMICAL AIR CONTAMINATION

Outdoor Chemical Air Pollution in Chicago

In general, outdoor chemical air pollution of metropolitan industrial regions is accentuated on quiet, humid, foggy, or rainy days. This type of weather is apt to be more common in winter and progressively less so in spring, fall, and summer. However, summertime is by no means a period free of air contamination. Automotive traffic is not only greater, but a given vehicle contaminates more air in hot weather because of the increased volatility of its exhausts, engine odors, and plastic and rubber installations.

Aside from the peculiarities of geography and weather previously mentioned, the problem of outdoor chemical air pollution presented by Chicago may be taken as an *example* of other large metropolitan areas. This city contains four major foci of outdoor chemical air pollution, important in the production and perpetuation of chronic symptoms in susceptible persons. The greatest of these localized sources, as judged by the clinical response of susceptible persons, is the petroleum refinery area at the extreme northern border of Illinois and Indiana. Another rapidly growing and similar refinery focus is in the area adjoining the ship canal southwest of Chicago. Another more diffuse focus, centers about a large paint manufacturing plant on the south side of the city, located near several heavy industries. The fourth area, even more diffuse, centers in the loop. Automotive and railroad traffic odors are its major contributors. Traffic-contaminated expressways and dieselized railroads extend peripherally in spoke-like fashion. Depending upon the direction and strength of the wind and certain other weather conditions, these foci frequently overlap, or the contaminated blanket of air overlying them is pushed in one direction or another. As previously mentioned, the concentration of these three manufacturing and refinery regions to the south, gives this portion of the city a relatively more constant atmospheric pollution than occurs in other areas.

Also, there are important vertical limitations of outdoor air pollution in this area. Downtown air pollution is worse at street level and in basements of downtown stores, although there appears to be little difference as far as the first few floors are concerned. Atmospheric contamination as a major factor in the production of symptoms in the susceptible individual ordinarily is not troublesome above the twentieth floor of loop buildings. Although present in subways, air contamination is not as excessive as might be expected because of the air turbulence.

The problem of outdoor chemical air pollution in this area is illustrated by the following case.

An architect with a history of advanced susceptibility to diverse chemical exposures, as manifested by rhinitis, coughing, headache, fatigue, mental confusion, and intermittent bouts of depression, lived in the first suburb west of Chicago. He commuted daily to the center of the city and for a full year kept a *log* on his *symptoms,* correlating them with *weather* conditions. The factors of *indoor* chemical air contamination and other chemical exposures had been limited as far as possible by a change of residence—an electrically equipped, warm-water-heated home having a detached garage; all sponge rubber, odorous plastics, and other indoor sources of contamination had been eliminated. He maintained a diet and water supply uncontaminated by chemicals and took no drugs. His home was in a residential area several blocks from industrial installations, railroads, or expressways.

In general, he remained more comfortable in his home than in his downtown office, even though storage of blue prints and other sources of air contaminants had been removed. But, significantly, even with the ideal home conditions, he remained symptom-free *only* when the wind was blowing from the west, northwest, and north. Invariably, he had a recurrence of symptoms in association with an east wind, which brought the Chicago air contaminants, and even more so with a southeast wind, bringing fumes from the industrialized refinery section. Even winds from the south and southwest were troublesome, yet this patient had no trouble with winds from any direction if blowing at the rate of *15 or more miles per hour.* The *most troublesome* were the "drift" winds from the southeast which blow between 3 and 7 miles per hour. This holds true for all patients susceptible to chemicals and reacting to outdoor air contaminants in this area.

This patient's *bad days* for the entire year not only checked with these weather conditions but also correlated with visibility as measured by the U. S. Weather Bureau.

There has been a long-standing need for more precise measurements of chemical air contaminants. Lacking such determinations, visibility—as measured by the distance one is able to see spaced lights—appears to be the best over-all indicator, as the problem has been studied clinically in this region.

To illustrate the carrying capacity of drift winds, refinery odors arising from extreme Northwestern Indiana may carry across the tip of Lake Michigan and cause impaired visibility and acute symptoms along the North Shore, 75 miles distant. Another similar drift wind at 5 miles per hour from the south-southwest carried detectable refinery odors from the Joliet region to Waukegan. Four highly susceptible patients in a line corresponding to a "cigar-shaped" shaded area of a fallout map were simultaneously *acutely ill* between 40 and 75 miles from the source of this contamination. Although these are unusual circumstances, it may be said conservatively that there is no residential area within a 50 miles radius of the center of Chicago which is consistently *free* from air contaminants arising from the city and environs. It should be noted that this statement considers only one aspect of the outdoor air contamination problem. Certain other chemical exposures are accentuated in suburban areas, as will be described.

Engine Exhausts

General Considerations.—From attempts to evaluate the clinical effects of motor exhausts on susceptible persons, the most immediate and acute reactions seem to result from *diesel* truck, bus, tractor, train, and boat exhausts. The next most common cause of acute reactions are the odorous and/or bluish-colored exhausts arising from *any* motor vehicle. This general type of exhaust characterizes operating *diesel* engines at *all* times; otherwise, it seems to arise principally from non-diesel engines in *poor mechanical adjustment* or repair and when mechanically satisfactory engines are *decelerating;* also when *first started in cold weather.* Diesel and non-diesel exhausts, arising from a relatively incomplete combustion of fuels, are especially noxious in precipitating acute intermittent reactions in susceptible persons. However, exhausts of gasoline-burning engines operating at maintenance speed, in view of their larger number, are probably greater sources of metropolitan air pollution and chronic symptoms.

Air contamination of major cities attributable to motor exhausts is generally heaviest in the central business and industrial districts. Spokes of contaminated air not only radiate peripherally to the open country, following the course of railroads, truck routes, bus lines, expressways, and other major traffic arterials, but also criss-cross such a metropolitan area. Foci of relatively greater air pollution, resulting from deceleration, occur at train stations and traffic stops. Although wind direction, velocity, and turbulence determine the degree of contamination at any given point, the fact remains that the closer a susceptible person lives to a city's central area, its major routes and "stop" intersections, the greater his *exhaust exposures.* This statement is based on the observation of the clinical effects on patients in many families advised to move from homes adjacent or near diesel railroads, truck or bus lines, expressways, and stop-light corners. Some highly susceptible individuals may have their chronic illness *perpetuated* from such exposures when living within three city blocks of major expressways.

In general, one may assume that if he is able to hear the *roar* of automotive traffic that he may also be reacting to the *fumes* of it, irrespective of whether he may be able to *detect* the odors. Conversely, the less the roar, the less the odor, since both tend to be carried by the same air movements.

Although directions for avoiding exposures to traffic odors will be outlined later, the basis for such recommendations will be discussed forthwith.

Diesel Exhausts.—Exposure of passengers on diesel trains to chemical fumes arising from the engine are greatest at points of entrance and exit from such trains. This is especially true of underground or covered stations in which passengers are forced to walk past a line of "purring" locomotives to reach their coach or the station exit. Train sheds designed for steam locomotives, having overhead apertures for carrying off smoke, are unsatis-

factory for diesel engines since these exhausts are relatively heavier than air and tend to settle. Some highly susceptible patients become acutely ill each time they attempt to run such a gauntlet. Other than this, passengers are apt to have less exposure to odors from riding on diesel-propelled trains than when traveling the same distance during rush hours by bus or automobile, although of course, there is considerable variation in the amount of exposure in different trains. When all common modes of transportation at ground level are considered, the electric elevated train, followed by the electric subway train, seems to be associated with the least pollution. Despite the tendency of certain traffic odors to settle in low places, air turbulence and ventilation in subways usually dissipate most of the odors that collect there.

Owing to the tendency of a moving vehicle to suck in its own exhausts through cracks and open windows, riders sitting in the rear of rear-engine diesel buses are more exposed to exhaust than those sitting or standing in front. This exposure is increased if favored by wind direction. The tendency for buses to follow each other closely also favors the entrance of exhaust of the lead bus into the passenger compartment of the following vehicle. Although this danger exists for any type of motor vehicle, it is especially marked in diesel buses and trucks. Despite the exhausts of propane-fueled buses causing far less acute reactions, these exhausts also are capable of producing identical reactions in susceptible persons if exposure is sufficiently great.

Passengers often develop headaches or other reactions during or following bus trips, without suspecting exhaust exposures. These effects usually are cumulative, often manifesting only after a certain mileage or time in the bus. In less susceptible persons, they may manifest only when riding in vehicles in poor mechanical repair or only when the rear windows are open. Localized reactions associated with such exposures are more often noted than the equally important *constitutional manifestations.* For example, the fatigue associated with riding the bus downtown and shopping is frequently out of proportion to the actual activity involved.

One particularly instructive patient developed fatigue and headache following each injection of house-dust extract, despite the elimination of chemical preservatives in the injected material and repeated reductions in dosage. The same reaction occurred after an injection of preservative-free normal saline, and again after the jab of a *dry* needle. Finally, after the same reaction occurred when the patient was turned back at the door *without receiving any injection,* the bus transportation was suspected. It was then learned that fatigue and headache did not occur when the trip was made by *elevated train* but invariably occurred following the trip by bus.

Another patient manifested abdominal cramps and diarrhea after riding a few blocks in a diesel bus, but was able to ride several miles in a propane-fueled bus before the onset of similar symptoms. Sleepiness and mental

confusion on bus trips is also a common manifestation of reactions in the chemically susceptible person.

Gasoline Exhausts.—Automobile passengers are far less exposed to exhausts when riding in the *front seat.* Rear-seat fume exposures are accentuated when rear side windows are open, especially so if the rear gate window of a station wagon is open. Eddy currents induced by the relative vacuum immediately behind a vehicle traveling above a certain critical rate of speed are extraordinarily effective in fouling the air in rear seats. Although the recent tendency of manufacturers to direct the exhausts of station wagons to the side is helpful, insucking of a station wagon's own exhaust remains a hazardous exposure.

Not only are susceptible passengers exposed to the exhausts of their own car and others in heavy traffic, but interior appointments in automobiles are also major sources of odors causing reactions in this group of patients. Rubber floor coverings, plastic upholstery, and sponge rubber cushions and padding are associated with reactions in susceptible persons in direct proportion to their odors. These sources usually are incriminated in the order named. Although a new automobile is usually more odorous in these respects than the same car after a period of use, the ability of these odors to induce reactions in susceptible persons is never entirely lost. In view of the marked differences between makes of cars as well as between models of the same manufacturer, a person with this illness should shop around until finding a new or used car in which he can ride in the open country comfortably. The "open country" is stipulated, for under these circumstances he is less apt to react to odors arising from *outside* his own vehicle.

In the writer's experience in supervising the purchase of automobiles for several extremely susceptible persons, this usually means *carpeting* instead of rubber floor coverings and *leather* or *nylon* upholstery and top interiors. Nylon, however, is not entirely safe, since it may cause reactions as a result of direct contact though not by inhalation. This will be discussed under a later heading.

Occasionally the odors arising from leaking anti-freeze, leaking brake fluids, heaters and rubber tires may be associated with similar reactions. Thus far, at least, plastic steering wheels and other hard plastics of the interiors of automobiles have not been incriminated as causes of inhalant reactions.

Hazardous Manifestations Owing to Traffic Odors.—A driver's impaired ability to operate a motor vehicle when either in chronic or acute reactions from chemical odors or fumes to which he is susceptible is *one of the most serious aspects of this medical problem.* Since chronic reactions are the most difficult to detect, these will be considered first. Rhinitis, coughing, asthma, gastrointestinal and other localized symptoms or such general effects as headaches, myalgia, or arthralgia are probably the most common.

Although these symptoms are distracting and have a considerable nuisance value, car sickness (nausea, vomiting with or without dizziness, and headache) is probably the most common. *Car* sickness should not be confused with *motion* sickness. It is of interest that this common manifestation of susceptibility to chemical odors and fumes is generally more pronounced in congested traffic than open country driving. Many victims of car sickness have learned empirically that they are less ill in the front than rear seats; some tolerate certain cars better than others in making an identical trip; several have been able to withstand the motion of elevated or cross-country electric trains without developing symptoms.

Potentially the most dangerous chronic reaction to the inhalation of odors and fumes is the gradual onset of fatigue and *overpowering sleepiness.* As this also usually occurs after several hours of exposure, it is exceedingly difficult—if not impossible—to differentiate from physical fatigue or even so-called driver hypnosis. Fatigue of the type occurring in these reactions is characterized by dopiness (impairment of memory, attention, concentration, and comprehension) as well as irritability.[6,18] Persons in such reactions tend to under-react in their ability to make quick decisions and to act on them. But they over-react in the sense that they tend to be easily annoyed by other persons and events. The latter sometimes manifests as extreme anger which, in a confused driver, may be directed toward another driver or car. Although these cutbacks in acuity of perception, association, and tolerance for the mistakes of others are serious enough, the *greatest single hazard* is the tendency for drivers suffering reactions to chemical additives and contaminants of air or food—or foods *per se—to doze off at the wheel.*

Whereas chronic reactions gradually impair perceptual and associative cerebral functions, acute reactions—usually resulting from more massive exposures—are apt to manifest themselves initially as impairment of *motor function* and *proprioception.* Irritability may be associated with either. The earliest symptoms of an acute reaction may consist of "nervousness," tenseness, blurring of vision, and lesser degrees of muscular incoordination. Although symptoms may not develop beyond this stage, it often progresses to general clumsiness characterized by over-reaching, under-reaching, and ataxia suggestive of intoxication. These drunk-like reactions also resemble alcoholic inebriation in that the reactor often presents a ruddy complexion, hoarseness, hyperactivity, and both a general tendency to *underestimate* the *degree of reaction* and to *overestimate the ability to drive.*

This parallelism may be carried even farther. The alcohol-inebriated person cannot tell the location of his feet unless looking at them. Drivers in this stage of chemically-induced cerebral reactions are inaccurate in gauging the force applied to the accelerator or brake—unless they look—and this is *even more hazardous.* Certain rapidly advancing acute reactions in the extremely susceptible (as illustrated in the foregoing case reports) may lead to loss of consciousness or convulsive seizures. However,

the majority of acute responses come on sufficiently gradually that a person, aware of his reacting in this manner, usually has time to protect himself before such a termination. Slowly progressing acute reactions taper off at any given level, first merging with and then being superseded by a corresponding level of more delayed chronic symptoms, as previously described.

Both chronic *effects* resulting from small cumulative exposures over an extended period of time and more *acute* reactions associated with greater exposures are believed to be responsible for a portion of the so-called "irreducible" human error in traffic accidents. Individuals with a known propensity for developing reactions of this type should drive less congested routes or always be accompanied by another person in the front seat who is capable of assuming control of the car in such an event. Another relatively under-emphasized danger in the case of a solitary driver finding himself slipping into a severe reaction is his tendency to *infract any traffic custom,* rule, or regulation hindering his escape from such a threatening situation before it overwhelms him. This is especially apt to occur in the lone driver caught behind a diesel vehicle or one in poor mechanical repair which is trailing a blue flume. This type of driving behavior on the part of a chemically susceptible person may so startle other drivers and pedestrians in the vicinity that a victim's zeal to flee from a bad situation leads to a worse one—an accident. These factors explain many traffic accidents which are reported merely as caused by the driver "going to sleep at the wheel."

What has been said about chronically dopey and/or acutely incoordinated driver's reaction to chemical additives and contaminants holds equally well for pedestrians wading through a ground-level blanket of urban smog. Indeed, this illness is so common that a driver can never assume a normal degree of perception and awareness of danger on a pedestrian's part nor his expected agility to escape from a threatening situation. The writer has seen patients so confused during reactions to chemical additives and contaminants, as well as to foods *per se,* that they changed their minds about crossing a street, reversing their course in the middle of it!

The chemically susceptible driver should also take particular care in refueling his car. Since most gasoline stations have multiple pumps approachable from various directions, after appraising the wind direction, he should drive into the station in a head-wind—as if landing an airplane. Then, after giving his instructions, he should either close the windows and remain inside or step away from the car as the tank is filled. The highly susceptible should not enter garages, especially body and paint shops. Certain individuals with unusually severe reaction potentialities should carry oxygen equipment in their cars at all times for use in case of emergencies. A more convenient and useful device is a cannister from a civilian gas mask containing activated carbon and equipped with Tygon* plastic tubing. By

*A special plastic manufactured for the food industry which is odorless and has been tolerated by these patients.

breathing through this home-made device, shown in Figure 1, which is equipped with an exhale valve in the tubing a few inches from the mouth aperture, one may pass through tunnels, follow diesel trucks or buses in traffic, or be subjected to massive airborne chemical exposures with impunity.

Fig. 1. An activated carbon filter for removing of air pollutants in use. When not in use, the non-odorous plastic tubing, containing an exhale valve, fits into the carrying case.

Fogging for Insect Abatement and Weed Control

A major factor contributing to outdoor air contamination of areas not generally fouled otherwise is the increasing practice of fogging for insect control near urban centers. Persons known to be intolerant to various chemical exposures associated with city living often move to the suburban countryside for their health, only to be "abated" without warning in the middle of the night! Having retired with bedroom windows open, a susceptible person's first warning of the presence of the municipally-financed mosquito-abatement spray rig may be a strangling cough or even an epileptic form seizure. The writer has been called out at night on several different occasions to resuscitate such patients. Susceptible persons protect themselves from abatement programs variously. Some have requested the local agency to give them advance notice when their area is to be treated so that they may choose between fleeing the region or enclosing themselves in their own homes. Some have moved farther into the country, but this

usually fails. Either a new agency is formed in this region, they run into trouble with farmers spraying for weed control, or foresters spraying for insect pests. A few have actually returned to the most livable part of the city from which they moved, finding its hazards less disturbing than the current indiscriminate spraying of the countryside.

Even while driving in the country, one may suddenly encounter roadside weed control spraying. The highly susceptible person is well advised to stop, turn around, and escape as rapidly as possible. An alternative move is to close his car windows and breathe through his activated carbon cannister. Even driving along a recently sprayed roadside or railroad right-of-way or through a country area immediately after spraying for weed or insect control, a person may experience a reaction.

Tar Roofing and Road Construction

A fuming tar trailer used in roofing and road construction or a recently tarred road also may provide this type of patient with a similar emergency. This should be handled as above described. When the roof, alley, road, or parking lot near one's home is being tarred, victims of this illness are advised to flee for a week or more. But upon returning and for at least a year following, during direct sun exposure, these areas remain a major source of both outdoor and indoor air contamination.

Miscellaneous Exposures

One occasionally encounters an odorous smudge from burning of old automobile tires, creosoted railroad ties or other chemically impregnated wood. The odors of such materials or those from burning dumps may constitute a major traffic hazard when occurring in close proximity to a traffic arterial. The fumes from burning paraffin-coated milk cartons and waxed food wrappers, in communities where dry garbage is incinerated locally, contribute to air pollution in general and to the ill health of susceptible persons. Similar reactions sometimes follow the burning of oil impregnated rags or other oily or chemically treated household debris.

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(To Be Continued)

A discussion of chemical additives of foods, water and biologic drugs, as well as chemical drugs and personal contacts, will appear in a later issue.

THE CLIMATIC TREATMENT OF BRONCHIAL ASTHMA

Historical Document

1888

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IF ONE seeks information on the selection of a suitable climate for an asthmatic patient, he will soon realize that no successful attempt has been made to establish indications for preference of one climate over another for any given case of asthma; that changes of climate have been made usually in an experimental way, and have been as likely to be attended with aggravation as relief to the symptom.

The chief cause of this is the mistake which has been made in trying to reduce all cases of asthma to one class, assuming that the ultimate cause and mode of development of this symptom were the same in all cases. This has led to the origin and promulgation of different theories, which have been in turn supported and abandoned. We find, in looking over the literature of the subject, that at one time asthma had been considered almost exclusively as a bronchial spasm of local origin, and treatment appropriate to this condition recommended; at another time, the theory of hyperaemia of local origin has received much favor; and at still another, the reflex origin (at one time of spasm, and at another of hyperaemia) has been dwelt upon.

This habit of the human mind, of looking at only a part of the truth, was characteristically urged by Dr. Daly in his paper at the last meeting of this Association. This is especially true of the medical mind, and the inevitable result of specialism in practice has been to increase this tendency.

The ease of error of the medical man is greater than that of the blind men in Tolstoy's fable, because, while he may soon learn to interrogate all parts of the animal brought to him for examination, he will also soon be made aware that there is a great variety of animals. The specialist is familiar with one kind of asthma, according to his field of practice. The asthmatics who go to a rhinologist are naturally those who have trouble in the nose; the asthmatics whose symptoms are wholly thoracic consult some one of repute in that field; and this leads to the result that Dr. Bosworth* tells us, that he has found evidence of intra-nasal disease in every case of eighty asthmatics on his note-books, in sufficient degree to warrant the conclusion that it exercised a powerful causative influence in the production of the asthmatic attacks.

It has also led Dr. Hyde Salter** to say that 80 per cent. *(sic)* of

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*American Journal of the Medical Sciences, Sept. 1888.

**On Asthma; its Pathology and Treatment. P. 78, New York, 1882.

cases of asthma in the young date from some acute inflammatory infection of the lungs, and has led Berkart to put the proportion due to this cause as high as 90 per cent.†

The dermatologist would tell us, perhaps, that he had seen asthma almost invariably associated with eczema, and the syphilogian might say that he had never seen a case of asthma without syphilis. The fact is, that asthma is only a symptom, and the factors whose combination produces a paroxysm are not always the same.

I should agree to the combination given by Dr. Bosworth as applying to a large class of cases, including most of the hay-fever cases. This combination was: (1) The neurotic habit. (2) A diseased condition of the nasal mucous membrane. (3) Some peculiar atmospheric condition, which precipitates the paroxysm; i.e., we have a predisposing, a determining, and an exciting cause. In order, however, to make this applicable to asthma in general, I should consider it necessary to make the second and third conditions more comprehensive. The second might be stated as a morbid condition somewhere in the respiratory tract, it may be in the upper air-passages or in the lungs themselves, whose irritation shows itself by a reflex exhibition in the bronchial tubes. The third condition should be made to include not only peculiar atmospheric states, but also digestive derangement, mental disturbances, and other remote irritations which act by reflex on the bronchial tubes.

It should always be borne in mind also that we may have more than one of the conditions mentioned under the second and third classes operative at once. For instance, we may have nasal disease and some change in the lung structure cooperating in the same patient, and also more than one of the exciting causes operative at the same time. This should lead us to be guarded in prognosis, and not to be too confident of cure because we have detected a single factor which is capable of removal. Who has not seen asthma persist after removal of nasal polypi, or after removal of a patient from a pollen-laden air which seemed to be the exciting cause of the attack?

In regard to the coexistence of different factors for the production of bronchial asthma it may probably be said that only the second and third are absolutely necessary, and that while the first (the neurotic habit) is a pretty constant factor, a paroxysm may be produced without it when the determining cause (second factor) is situated in the lung itself. In considering the effect of climate upon the paroxysm it can readily be seen that its effect upon each of the factors should be studied separately; and, if either factor can be eliminated or seriously modified by climatic change, then the attacks will cease.

It thus becomes more explicable why entirely different climates relieve different cases of asthma, or even the same case at different times. Who has not seen a patient completely relieved by a change of climate for a number

†On Asthma; Its Pathology and Treatment. London, 1878.

of years, perhaps, and afterward, the symptoms returning, be again relieved by another move, perhaps even back to the starting point? Now, in such a case it is very likely that the patient, while strengthened in one factor, was gradually weakened in another until the paroxysm was again developed, to be again prevented by a variation of influence.

When, therefore, a case of bronchial asthma presents itself to us, and we are called upon to break the "vicious combination," we try to determine which of the essential factors is most easily removed or modified.

The third factor (the exciting cause) is the one which is apt to engage the attention first, and it may be oftentimes easily removed. When the exciting cause is atmospheric, it may be some variation in the proper constitution of the air, or it may be the presence of accidental emanations, as the pollen of plants, the odor of animals, or animal or vegetable products. When the latter condition obtains and is once recognized, the patient may be able to keep himself out of the reach of the excitant, and, as is well known, an army of hay-fever subjects keep themselves well in this way by an annual exodus to exempt districts.

The well-known susceptibility of asthmatics to paroxysms in the country as compared to the city may likewise sometimes depend upon the presence of vegetable or animal emanations in the country air. In other cases, it seems to be the atmosphere containing the most carbonic acid which affords the most relief; hence, the old, crowded portions of the city are looked upon by certain asthmatics as the abodes of bliss. This accords with the recent reports of cases of "dyspnoea" relieved by inhalations of carbonic acid gas.

A change in the density of the air sometimes affords marked relief. It is well known that removal to a high altitude relieves certain cases. These may be such as have for a determining cause some morbid condition of the bronchial area, in which a slight superficial hyperaemia and relative internal anaemia may relieve the paroxysm, and the variation in pressure at different altitudes may be enough to determine this. Instances of digestive derangement and nervous disturbance as exciting causes of asthmatic attacks are too well known to need illustration. I once had a gentleman patient recently married who almost always had an attack on sexual intercourse. I had another patient who could stop an attack by gambling for high stakes.

In regard to the possibility of so modifying the second factor (a morbid condition somewhere in the respiratory tract, which may be called the determining cause) that the combination shall fail, it may be said that this is sometimes easy and sometimes impossible. When the lesion is accessible to operation, as in the nose, this may be easy; when it is below the reach of operative methods, it may be very difficult or impossible. Perhaps the most brilliant results in the latter field are seen in the cures wrought by the potassium iodide. This remedy is especially efficacious in those cases in

which there is evidently a catarrhal inflammation of the bronchial mucous membrane. These cases are also quite susceptible to a proper change of climate—i.e., such a change as we have reason to believe would benefit the bronchial or pulmonary lesion. As to the possibility of so modifying the first factor as to prevent the attacks, I should say that while we may sometimes be successful in warding off the paroxysm by fortifying the nervous system with good hygiene and specific tonics, we will be less successful in this mode of attack than in either of the others. So, also, we may occasionally, in cases in which the neurotic factor is a prominent one, succeed in so modifying it by change of residence as to effect a cure in this way.

So it will appear that in climatic, as in medical, (*sic*) treatment we must make our application to the ascertained condition of the patient, as far as it is possible to diagnosticate this, and not to the name of a disease. There is no climate which is good for all cases of asthma, and we must carefully consider, when a patient presents himself for treatment, the nature of these three factors in his case, and which of them we intend to modify, and how far change of climate may be able to aid us in this.

FOLLOW THE ORDER OF NATURE

Let things work themselves out. The same Order of Nature that provides for fleas and for molds will provide also for men who have as much patience as fleas and molds to put themselves under its gouvernance. We get nowhere by shouting, Gee! and Haw! This is all very well to get hoarse, but it does not get us ahead.

The Order of Nature is proud, and it is pitiless. Our fears, our despairs disgust it, and only keep it from coming to our aid, instead of inviting it. It owes its source to illness as well as to health. Bribes for the one and against the other, it will not take. That is confusion. Follow the Order of Nature, for God's sake! Follow it! It will lead who follows; and those who will not, it will drag along anyway, and their tempers and their medicines with them. Get a purge for your brain. It will do better for you than for your stomach.—*Essays*, M. E. DeMontaigne, 1533-1592.

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Although triethylene melamine may result in pancytopenia, its use is suggested for inoperable undifferentiated carcinoma of the lung because the blood abnormality can be treated by means of corticosteroid hormones and infections by penicillin. Some patients may need whole blood transfusions.

Garrett, E. R.: The physical chemical evidence for aspirin anhydride as a superior form for the oral administration of aspirin. J. Am. Pharm. Assoc. (Sci. Ed.), 48:676 (Dec.) 1959.

As a result of physical, chemical and kinetic investigations, it is concluded that aspirin anhydride releases acetylsalicylic acid, and yet causes no digestive tract disturbances because there are no particles of undissolved acetylsalicylic acid adherent to gastric or intestinal mucosae.

Books of Interest

AN ATLAS OF BRONCHOSCOPY. By A. Huzly, M.D. 180 pages, 180 illustrations. New York: Grune and Stratton, 1960.

This atlas presents bronchoscopic photographs to illustrate the principal changes in those parts of the tracheo-bronchial tree which are open to endoscopic examination. In selecting 180 pictures out of a collection of about 1,000 color slides, some of the rarities as well as many anatomical variations had to be omitted. Nevertheless, it is hoped that the subject of bronchoscopic diagnosis has been adequately illustrated by these representative pictures. The author is fortunate in being in charge of both the thoracic surgery and the bronchology departments of the Sanatorium Schillerhöhe. As a result, he has been able to compare the bronchoscopic appearances (as well as the bronchograms and tomograms) with the actual findings at thoracotomy in 1,500 cases, and with the resected specimen in 1,200 cases.—AUTHOR'S PREFACE

News Items

SECTION ON ALLERGY, CONNECTICUT STATE MEDICAL SOCIETY

At a recent meeting, the members of the Section on Allergy of the Connecticut State Medical Society elected the following officers for the 1961 term:

President—Irving H. Krall, Hartford
Vice President—John F. Beakey, Hartford
Secretary-Treasurer—Marvin Mogil, New Haven

WOMEN'S AUXILIARY MEMORIAL SCHOLARSHIPS

The Women's Auxiliary of the American College of Allergists announces its contribution of $300 to the College for scholarships to the Graduate Instructional Course of the Eighteenth Annual Congress, April 1-3, 1962, at Minneapolis, Minnesota. These scholarships will be awarded in accordance with the order in which applications are received and on the basis of the merit of the applications. Physicians who wish to be considered for these scholarships should send their applications to Dr. Mayer Green, Program Chairman, 6111 Jenkins Arcade, Pittsburgh, Pennsylvania.

TWELFTH INTERNATIONAL CONGRESS OF DERMATOLOGY

The International Committee of Dermatology announces that the Twelfth International Congress of Dermatology will be held in Washington, D. C., in 1962.

All those wishing information and directions concerning the making or submitting of material for filmed or televised case presentations are urged to send their requests immediately to Dr. Marion B. Sulzberger, Chairman, Committee on Film Case Presentations, 999 Fifth Avenue, New York 28, New York.